American Heart Journal

VOL. 54 November, 1957 No. 5

Editorial

A SURGEON'S VIEW OF ATHEROSCLEROSIS

Atherosclerosis has been of interest for more than a century and the characteristic morphologic changes are well known; yet its etiology remains obscure. Within the past 5 years operations have been developed for replacement or bypass of segments of the aorta and peripheral arteries involved in two major complications of atherosclerosis, namely, aneurysms and occlusive disease. Treatment of these conditions has afforded the surgeon an unusual opportunity to study atherosclerosis in the dynamic state, and from this experience certain random observations have been made.

From arteriographic studies and observations made at operation, it is apparent that atherosclerosis is far more common in young adults than previously recognized. Formerly, it was assumed that symptoms of ischemia in the lower extremities appearing before the age of 40 were due to thromboangiitis obliterans, while those beginning after 40 were a result of atherosclerosis. It is evident now that a majority of patients with occlusive arterial disease are victims of atherosclerosis, irrespective of age, and that thromboangiitis is a rare condition indeed.

The syndrome of aortoiliac occlusion described by Leriche consists of complete occlusion of the aortic bifurcation, resulting in symptoms of ischemia in the lower extremities, sexual impotence, and hypertension. Actually, there are two types of aortic occlusive disease, depending upon the degree of obliteration of the lumen. In the incomplete type, atheromatous mural deposits narrow the lumen to a point where significant reduction in blood flow occurs. In complete occlusion, distal blood flow occurs solely by way of collaterals. Measurements of pressure above and below the involved aortic bifurcation reveal a reduction of 50 per cent or more in the systolic component below the completely obliterated segment, whereas in incomplete occlusion, the gradient is only 10 to 15 per cent. This difference appears to be significant in view of the infrequent occurrence of peripheral atherosclerosis in patients with complete aortic occlusion and its frequency in those with incomplete occlusion. It suggests that arterial tension may be a factor in the formation of atheromas; that is, at normal or elevated arterial pressures atheromas develop, whereas at pressures below a critical level these lesions are not formed. In a few instances restoration of aortic continuity following resection of a completely occluded bifurcation has actually been followed, within months, by the appearance of atherosclerotic lesions in distal peripheral arteries.

Utilization of homologous arteries to replace segments of the aorta and peripheral arteries in the treatment of aneurysms and occlusive disease has afforded an unusual opportunity to explore the concept that a systemic metabolic factor is active in the pathogenesis of atherosclerosis. Thus, if a metabolic factor exists,

Received for publication July 8, 1957.

transplantation of a graft free of atherosclerosis into an arterial system severely involved with this process might result in the development of atheromatous lesions in the transplant. Conversely, grafts implanted into individuals free of atherosclerosis would also remain free of this disease. Experimental and clinical studies support this concept. Thus, canine homografts examined 4 to 5 years after transplantation show none of the characteristic morphologic changes of atherosclerosis although calcific deposits are numerous. However, when dogs are maintained in a hyperlipemic state, abdominal aortic homografts become sites of predilection for atheromatous change. Recently, four human aortic homografts were examined 1 to 2½ years after transplantation to patients with atherosclerosis. Of these specimens, three revealed atheromatous lesions indistinguishable from those in the adjacent aorta.

The procedure of thrombointimectomy likewise provides an opportunity to investigate the concept of a metabolic pathogenetic factor. This technique consists in the removal of mural thrombotic and atherosclerotic material by developing a plane of cleavage between the inner layers of the arterial wall and the remaining, more normal layers. Usually this separation takes place within the inner or middle third of the media. Once the diseased layer is mobilized, it is excised and arterial continuity restored.

Examination of the aorta or peripheral artery months or years after thrombointimectomy reveals, in some instances, a recurrence of atheromas on the arterial wall previously freed of these lesions. In fact, in some cases the recurrent lesions are so numerous and resemble so closely those in the adjacent vessel that the area in which thrombointimectomy was performed is not readily recognized.

These observations are of significance only as they suggest new methods for studying atherosclerosis. For example, the relation of arterial tension to development of atheromas should be investigated experimentally. Coarctation of the abdominal aorta could be produced in the dog and hyperlipemia maintained. Development of atheromas in the high and low pressure segments of the aorta (above and below the coarctation) then could be compared.

Many patients operated upon for aneurysms and occlusive disease are in the later decades of life and have a relatively short life expectancy. Thus, the time from operation to death is an opportunity to investigate certain aspects of lipid metabolism as it relates to atherosclerosis. At operation, the diagnosis of atherosclerosis could be made with certainty and the type and extent of the atheromatous lesions recorded. Subsequently, at necropsy, whether months or years later, the arterial system could be re-examined and the findings compared with those obtained previously. Thus, a series of "before and after" observations would be available against which factors such as the natural history of the disease, metabolic alterations, and effectiveness of drug therapy could be evaluated. To a surgeon, at least, this sort of investigation is more appealing than one in which the diagnosis is based solely upon clinical manifestations, the electrocardiogram, and blood lipids, and in which the same indirect criteria are employed in evaluating results.

Oscar Creech, Jr., M.D.*

*The William Henderson Professor of Surgery, and Chairman of the Department of Surgery, Tulane University School of Medicine, New Orleans, La.

Original Communications

PYRIBENZAMINE (TRIPELENNAMINE): EFFECTS ON RENAL HEMODYNAMICS AND THE EXCRETION OF WATER AND ELECTROLYTES

JOHN H. MOYER, M.D.,* JACK BURGESS, M.D., AND RALPH V. FORD, M.D.

WITH THE TECHNICAL ASSISTANCE OF
JEAN GAFFNEY, CAROL HOUSE, AND ANN HALL

HOUSTON, TEX.

THE antihistaminic properties of tripelennamine (Pyribenzamine) are well documented, and in this role the agent enjoys widespread therapeutic popularity. Recently, application of antihistaminic substances to the field of surgery has been suggested, based upon the rationale of tissue response inhibition. An additional property of diuretic activity has been ascribed to Pyribenzamine (tripelennamine) and other antihistaminics by several reports appearing in the literature.[1-6] Of particular interest is a report that this drug potentiates the diuretic response to organo-mercurials.

In the light of these developments, it seemed that an investigation of the renal hemodynamics of Pyribenzamine would be of value. The purpose of this report is to present observations, both in the laboratory and in man, on the changes in renal hemodynamics and the excretion of water and electrolytes due to the administration of Pyribenzamine.[6]

METHODS AND MATERIALS

Laboratory Observations.—Mongrel dogs, anesthetized with 30 mg./Kg. of pentobarbital sodium and weighing 10 to 20 kilograms, were used for the laboratory experiments. Two groups of dogs were studied. Group I consisted of 10 hydrated dogs on which glomerular filtration rate, renal plasma flow, renal blood flow, blood pressure, hematocrit, and water and electrolyte excretion were determined. Observations were made before, immediately after, and 1 hour after the intravenous administration of 25 or 50 mg. of Pyribenzamine. Control values were obtained by taking the average of 3 consecutive 10-minute periods. After the intravenous administration of Pyribenzamine, consecutive 10-minute urine collection periods were obtained for 1 hour or more. Methods and techniques have been described previously.[7]

From the Department of Pharmacology, Baylor University College of Medicine, Houston, Tex.
Supported in part by a grant from the Houston Heart Association.
Received for publication April 1, 1957.
*Currently Professor of Medicine, Hahnemann Medical College, Philadelphia, Pa.

TABLE I. EFFECT OF INTRAVENOUSLY ADMINISTERED PYRIBENZAMINE (25 MG.) ON RENAL HEMODYNAMICS AND ON WATER AND ELECTROLYTE EXCRETION IN DOGS

DOG NUMBER	WEIGHT (KG.)	PYRIBENZAMINE DOSE (MG.)	MEAN BLOOD PRESSURE (MM. Hg)			GLOMERULAR FILTRATION RATE (C.C./MIN.)			RENAL PLASMA FLOW (C.C./MIN.)			RENAL BLOOD FLOW (C.C./MIN.)			HEMATOCRIT			URINE VOLUME (C.C./MIN.)			PLASMA SODIUM (MEQ./L.)			PLASMA POTASSIUM (MEQ./L.)			URINE SODIUM EXCRETION (μEQ/MIN.)			URINE POTASSIUM EXCRETION (μEQ/MIN.)		
			C	D_1†	D_2	C	D_1†	D_2	C	D_1†	D_2	C	D_1	D_2	C	D_1	D_2	C	D_1	D_2	C	D_1	D_2	C	D_1	D_2	C	D_1	D_2	C	D_1	D_2
1	11.0	25	147	160	154	59	49	55	189	131	140	357	273	280	47	52	50	2.5	2.5	3.1	131	131	131	2.7	3.4	2.6	96	56	86	35	28	34
2	11.6	25	122	152	177	26	23	25	90	63	61	158	111	109	43	43	44	1.5	1.2	3.0	140	141	139	2.7	3.6	3.4	89	46	65	28	26	24
3	10.0	25	141	145	137	37	34	43	135	144	148	250	313	302	46	54	51	0.7	0.6	1.5	135	133	130	2.9	3.6	4.1	30	35	60	14	16	34
4	20.0	25	84	98	114	60	41	71	169	118	145	376	251	337	55	53	57	0.7	0.4	1.1	139	140	140	3.4	3.5	3.5	16	5	24	39	25	51
5	18.0	50	143	147	153	61	62	59	184	162	175	376	345	365	51	53	52	7.2	5.4	6.9	136	136	144	3.0	4.1	3.5	127	79	69	40	37	47
6	14.4	50	111	142	136	11	10	11	117	80	97	198	140	164	41	43	41	0.9	1.1	2.9	139	139	139	3.1	3.1	3.1	103	26	47	40	32	39
7	10.5	50	142	147	151	39	41	44	105	120	117	169	200	195	38	40	40	0.4	0.9	1.5	141	140	137	3.3	3.5	2.8	77	96	171	37	27	43
8	12.0*	50	93	118	98	40	34	13	183	142	45	295	241	79	38	41	43	0.4	0.4	0.2	140	137	137	3.3	2.9	2.4	7	7	6	21	16	3
9	10.0	50	104	93	95	38	29	31	110	105	107	177	184	178	38	43	40	1.0	0.6	0.9	131	131	131	2.4	2.3	2.1	74	13	12	24	12	17
10	13.5	50	93	99	108	33	24	36	160	120	134	267	226	253	40	47	47	0.8	0.5	0.7	131	131	130	3.2	3.0	2.9	393	119	114	25	12	17
Mean			118	130	132	40	35	39	144	119	117	262	228	226	44	47	47	1.6	1.4	2.2	136	136	136	3.0	3.3	3.0	101	48	65	30	23	31
Per Cent of Control				110	112		88	98		83	81		87	86		107	107		88	138		100	100		110	100		48	64		77	103
P Value‡ <				.05	.05		.05	.50		.01	.01		.10	.20		.05	.01		.20	.10		.40	.50		.10	.50		.01	.30		.01	.50

C = Control: Average of three 10-minute periods. D_1 = Immediately after administration of Pyribenzamine (average of three 10-minute periods). D_2 = Observations made 1 hour after administration of Pyribenzamine (average of two 10-minute periods).

*Dog died 18 hours after Pyribenzamine was administered.

†In the first period after Pyribenzamine was administered there was always a sharp rise in blood pressure, with a marked reduction in GFR and RPF which usually returned towards normal by the second and third postdrug period.

$$\ddagger t = \bar{x}\sqrt{\frac{n(n-1)}{S_x^2}}$$

Group II consisted of 25 dogs on which observations of water and electrolyte excretion were made (concurrent renal function studies were not done). Control values were determined by obtaining 3 urine collection periods of 20 minutes each. Twenty-five milligrams of Pyribenzamine were then given intravenously, following which observations were made for a period of 2 hours employing 20-minute periods similar to the control observations. Nineteen of the dogs (Subgroup IIA) were not hydrated prior to the study (Table II) and 6 of them (Subgroup IIB) received a steady infusion of 5 per cent glucose (Table III) for 2 hours before administration of the drug and throughout the period of observation.

Clinical Observations.—Clinical observations were made on 4 groups of patients. Group 1 consisted of 10 patients with mild heart failure on whom bio-assay studies were done using water and sodium excretion as an estimate of diuresis. These studies were conducted on a metabolic ward, using patients who were edema-free at the time of the study. They drank 3,000 ml. of distilled water per 24 hours and ate a diet containing 50 mEq. of sodium per 24 hours. Twenty-four-hour urine specimens were collected and analyzed for sodium. The patients were weighed each morning before breakfast and after voiding. After suitable control periods the patient's urinary output of sodium was stable, being approximately 90 to 95 per cent of the dietary sodium intake. The patient's excretion rate of sodium continued at this constant level for at least 3 days. The patient was then given 50 mg. of Pyribenzamine every 6 hours. The body weight and excretion rates of sodium and water were determined during this 24-hour period of drug administration.

Group 2 consisted of 5 patients with mild heart failure on whom renal function studies were done employing methods and techniques previously described.[8] Inulin was used to determine glomerular filtration rate and para-aminohippurate to determine renal plasma flow. Three consecutive 10-minute urine collection periods were used for the control observations. Consecutive 10-minute urine collection periods were obtained for 3 hours following the intravenous administration of 50 mg. of Pyribenzamine.

Group 3 consisted of 3 patients with mild congestive heart failure (due to hypertension) who were studied under metabolically controlled conditions for 18 to 25 days with constant water and sodium chloride intake. After equilibration and stability of weight were obtained, they were given an intramuscular injection of the organic thio-mercurial diuretic, diglucomethoxane (Mersoben*) in a dose equivalent to 40 mg. of mercury. After an appropriate interval (at least 48 hours) 50 mg. of Pyribenzamine was given intramuscularly. Subsequently, Pyribenzamine (50 mg.) plus diglucomethoxane (40 mg. Hg equivalent) were given on the same day. This cycle was repeated 3 to 5 times in each patient. Observations of the excretion rate of water, sodium, potassium and chloride and the body weight were made as outlined above.

Group 4 was composed of only 2 patients (both third decade Negro men) with the nephrotic syndrome of glomerulonephritis who were studied for acute changes in renal hemodynamics and the excretion of water and electrolytes following the intravenous administration of 25 mg. of Pyribenzamine. The studies were conducted as on the patients in Group 2.

RESULTS

Laboratory Observations.—The effects of 25 mg. of Pyribenzamine administered intravenously to dogs are presented in Tables I to III. Table I is the tabulation of renal function data and Tables II and III contain only data on water and electrolyte excretion.

Immediately after the administration of the drug there was an increase in blood pressure ($p < 0.05$) associated with a slight reduction in glomerular filtration rate ($p < 0.05$) and renal blood flow ($p < 0.10$). Glomerular filtration rate usually returned to normal within 1 hour after drug administration, but the blood pressure remained elevated and the renal blood flow remained slightly ($p < 0.20$)

*Available from Ciba Pharmaceutical Products, Inc., Summit, N. J.

depressed. There was a significant increase in the hematocrit ($p < 0.05$) as well as a moderate but temporary decrease in the excretion of sodium without a significant change in the urine volume.

In the second group of dogs (Table II), those which did not receive an infusion, there were no statistically significant alterations in the excretion of water ($p > 0.50$), sodium ($p < 0.10$), or potassium ($p < 0.30$). Likewise, the plasma concentrations of sodium and potassium were not affected.

In the animals in Group IIB, those which received continuous infusions of 5 per cent glucose (Table III), Pyribenzamine tended to increase sodium and water excretion, but here again the response was not statistically significant.

Clinical Observations.—The bio-assay studies which were done under controlled metabolic conditions (Table IV) indicated that there was a slight over-all increase in sodium and water excretion following the administration of Pyribenzamine to patients in heart failure; but, as in the animal experiments, this response was inconstant and was not statistically significant ($p > 0.10$).

The renal hemodynamic effects of 25 mg. of Pyribenzamine administered intravenously to the patients in Group 2 (mild congestive heart failure) are

TABLE II. THE EFFECT OF 25 MG. OF PYRIBENZAMINE (GIVEN INTRAVENOUSLY) ON WATER AND ELECTROLYTE EXCRETION IN DOGS WHICH DID NOT RECEIVE AN INFUSION

DOG NUMBER	BODY WEIGHT (KG.)	URINE VOLUME (C.C./MIN.)				URINE SODIUM (μ EQ/MIN.)				URINE POTASSIUM (μ EQ/MIN.)			
		C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3
1	10.0	0.23	0.37	0.37	0.37	20	21	41	36	6	4	8	8
2	11.0	0.14	0.10	0.20	0.20	5	9	16	9	3	5	4	2
3	13.0	0.52	0.41	0.51	0.51	111	142	148	150	12	17	7	7
4	12.5	0.24	0.30	0.36	0.20	9	26	41	24	8	18	17	16
5	10.0	0.26	0.22	0.26	0.22	5	5	4	5	8	13	6	15
6	11.0	0.26	0.33	0.32	0.21	11	30	32	18	4	9	10	10
7	10.0	0.13	0.24	0.21	0.24	11	12	8	8	6	7	7	5
8	10.0	0.88	0.32	0.34	0.31	10	21	25	14	3	3	5	6
9	12.0	0.30	0.34	0.26	0.21	10	11	11	15	9	8	12	24
10	16.0	0.20	0.36	0.32	0.20	9	10	5	9	11	15	6	14
11	16.5	0.31	0.36	0.21	0.30	33	6	6	13	53	30	20	65
12	10.0	0.24	0.33	0.34	0.38	4	2	2	2	13	8	12	19
13	11.0	0.11	0.21	0.20	0.33	9	21	13	15	2	3	2	4
14	11.0	0.22	0.30	0.36	0.38	13	21	28	25	4	4	5	6
15	13.0	0.16	0.30	0.26	0.53	17	29	16	11	2	5	3	3
16	11.0	0.10	0.28	0.24	0.26	5	9	7	9	6	6	3	4
17	11.0	0.11	0.16	0.22	0.36	6	6	5	12	5	5	5	7
18	13.0	0.20	0.24	0.31	0.44	25	25	22	26	2	2	2	2
19	14.0	0.37	0.43	0.30	0.32	48	53	42	42	19	7	2	2
Mean	11.9	0.26	0.29	0.29	0.31	19	24	25	23	9	9	7	12
% of Control			112	112	119		126	132	121		100	78	133
P Value* <			.50	.50	.50		.10	.10	.20		.50	.40	.30

C = Control—average of three 20-minute periods. D_1 = Average of two 20-minute periods immediately after drug administration. D_2 = Average of two 20-minute periods taken 1 hour after drug administration. D_3 = Average of two 20-minute periods taken 2 hours after drug administration.

*Statistical analysis by R. A. Seibert.

presented in Table V. There was a slight but not statistically significant reduction in glomerular filtration rate and no effect on renal blood flow. The excretion of water decreased slightly and the urinary to plasma (concentration) ratio of

TABLE III. EFFECT OF 25 MG. OF PYRIBENZAMINE ON WATER AND ELECTROLYTE EXCRETION*

DOG NUMBER	DOG WEIGHT (KG.)	URINE VOLUME (C.C./MIN.)			SODIUM EXCRETION (μEQ/MIN.)			POTASSIUM EXCRETION (μEQ/MIN.)			PLASMA SODIUM (MEQ./L.)		PLASMA POTASSIUM (MEQ./L.)		INFUSION RATE 5% GLUCOSE (C.C./MIN.)
		C	D_1	D_2	C	D_1	D_2	C	D_1	D_2	C	D_1	C	D_1	
1	12.2	1.4	1.9	3.4	8	7	14	6	2	3	147	144	3.4	2.8	3.4
2	17.0	5.2	6.1	4.0	41	82	93	4	10	56	144	—	3.5	—	5.0
3	16.2	0.5	0.4	0.6	23	19	27	14	3	3	151	—	3.4	—	4.0
4	13.4	4.1	2.8	3.6	68	61	50	9	6	7	146	140	3.8	2.9	3.3
5	19.4	1.5	3.5	8.2	31	24	48	13	12	20	141	134	3.7	3.2	4.0
6	21.0	4.5	6.1	6.1	50	93	90	50	35	37	143	143	3.0	3.0	5.0
Mean	16.5	2.9	3.5	4.3	37	48	54	16	11	21	145	140	3.5	3.0	
P Value <			.40	.40		.50	.20		.20	.50		.20		.50	

C = Control: Average of three 10-minute periods. D_1 = Average of two 10-minute periods 10 to 30 minutes after Pyribenzamine administration intravenously. D_2 = Average of two 10-minute periods taken 1 hour after Pyribenzamine administration.

*Concurrent renal function studies not done.

TABLE IV. EFFECT OF PYRIBENZAMINE ON SODIUM EXCRETION AND WATER EXCRETION (IN PATIENTS WITH MILD HEART FAILURE)

PATIENT (GROUP 1)	SODIUM EXCRETION (MEQ./24 HRS.)			WATER EXCRETION (L./24 HRS.)		
	C	D	I	C	D	I
1	40	69	29	3.1	3.2	0.1
2	50	43	−7	2.8	3.0	0.2
3	43	70	27	3.2	2.8	−0.4
4	57	108	51	2.9	3.3	0.4
5	57	48	−9	3.1	3.0	−0.1
6	38	75	37	2.9	3.1	0.2
7	44	68	24	2.9	3.1	0.2
8	50	37	−13	3.2	2.9	−0.3
9	46	60	14	3.1	3.2	0.1
10	45	45	0	3.1	3.2	0.1
Mean	47	62	15	3.03	3.08	0.05
% of Control		133	32		102	2
P Value* <			NS			NS

*$P - t = \bar{x} \sqrt{\frac{n(n-1)}{S_x^2}}$; NS = Not statistically significant ($p > 0.10$).

C = control; D = drug; I = difference between the control value and the postdrug value.

inulin increased. There was also a slight decrease in the excretion of sodium but not of potassium. These responses of sodium and water excretion were similar to the responses in the animal experiments.

The 3 men in congestive heart failure (Table VI) who received a mercurial diuretic, diglucomethoxane (Mersoben), demonstrated the usual response of an increased excretion of chloride and sodium and, to a lesser extent, of water. When Pyribenzamine (25 mg. intravenously) was administered alone, no significant changes were observed in the excretion of water or electrolytes. When Pyribenzamine and the Mersoben were administered concurrently, the response in sodium and water excretion was no greater than when diglucomethoxane was given alone. This indicates that Pyribenzamine induces no diurectic activity when given either alone or in combination with a mercurial diuretic to patients in heart failure.

Two patients with the nephrotic syndrome received Pyribenzamine. Observations were made on the renal hemodynamic response to the drug. Glomerular filtration rate and renal blood flow were not altered, nor were the excretion rates of sodium and chloride altered significantly.

TABLE V. THE EFFECT OF INTRAVENOUS PYRIBENZAMINE ON RENAL HEMODYNAMICS AND THE EXCRETION OF WATER AND ELECTROLYTES

	GLOMERULAR FILTRATION RATE (C.C./MIN.)				RENAL PLASMA FLOW (C.C./MIN.)		RENAL BLOOD FLOW (C.C./MIN.)	
	C. IN.		C. CR.					
	C	D	C	D	C	D	C	D
Mean	81	75	87	83	509	503	789	785
% of Control		93		95		99		99
P Value*		NS		NS		NS		NS

	URINE VOLUME (ML./MIN.)		SODIUM EXCRETION (μEQ/MIN.)		POTASSIUM EXCRETION (μEQ/MIN.)		FILTRATION FRACTION × 100	
	C	D	C	D	C	D	C	D
Mean	6.3	4.3	121	88	51	51	16	16
% of Control		68		73		100		100
P Value*		NS		NS		NS		NS

$$*P - t = \bar{x}\sqrt{\frac{n(n-1)}{S_x^2}}$$

NS = Not statistically significant ($p > 0.10$); C = control observations; D = observations after drug administration; C. In. = clearance of inulin; C. Cr. = clearance of creatinine.

TABLE VI. THE EFFECT OF DIGLUCOMETHOXANE (MERSOBEN) AND TRIPELENNAMINE (PYRIBENZAMINE), GIVEN INTRAVENOUSLY, ON WATER AND ELECTROLYTE EXCRETION*

DRUG	WEIGHT CHANGE (KG.)			CHLORIDE EXCRETION (MEQ./24 HRS.)			POTASSIUM EXCRETION (MEQ./24 HRS.)			SODIUM EXCRETION (MEQ./24 HRS.)			WATER EXCRETION (L./24 HRS.)		
	C	D	I	C	D	I	C	D	I	C	D	I	C	D	I
Diglucomethoxane	91.9	91.2	−0.7	27.6	106.6	+ 79.0	63.5	79.0	+15.5	35.1	115.8	+ 80.7	3.52	4.63	+1.11
(Mersoben)	83.3	82.6	−0.7	22.4	217.6	+195.2	63.3	47.8	−15.5	26.9	218.3	+191.4	3.40	4.15	+ .75
(SU-1775)	105.8	103.0	−2.8	20.6	261.7	+241.1	44.7	61.3	+16.6	18.8	355.9	+337.1	1.99	4.10	+2.11
Average	93.7	92.3	−1.4	23.5	195.3	171.8	57.2	62.7	5.5	26.9	230.0	203.1	2.97	4.29	1.32
% of Control		99.0			831.0			110.0			855.0			144.0	
P Value <		NS			.01			NS			.05			.05	
Tripelennamine	91.9	91.6	−0.3	27.0	32.2	+ 5.2	63.5	64.9	+ 1.4	35.1	37.8	+ 2.7	3.52	3.53	+ .01
(Pyribenzamine)	83.3	84.0	+0.7	22.4	17.7	− 4.7	63.3	64.4	+ 1.1	26.7	27.0	+ 0.3	3.40	3.37	− .03
	105.8	105.2	−0.6	20.6	17.8	− 2.8	44.7	27.6	−17.1	18.8	2.8	− 16.0	1.99	1.57	− .42
Average	93.7	93.6	−0.07	23.3	22.6	− 0.8	57.2	52.3	− 4.9	26.9	22.5	− 4.3	2.97	2.82	− .15
% of Control		100.0			97.0			91.0			84.0			95.0	
P Value <		NS			NS			NS			NS			NS	
Diglucomethoxane	91.9	91.4	−0.5	27.0	187.3	+160.3	63.5	93.4	+29.9	35.1	194.8	+159.7	3.52	4.75	+1.23
+	83.3	82.6	−0.7	22.4	164.6	+142.2	63.3	48.9	−14.4	26.9	172.7	+145.8	3.40	3.82	+ .42
Tripelennamine	105.8	105.8	0	20.6	346.0	+325.4	44.7	76.4	+31.7	18.8	324.1	+305.3	1.99	4.67	+2.68
Average	93.7	93.3	−0.4	23.3	232.6	209.3	57.2	72.9	15.7	26.9	230.5	203.6	2.97	4.41	1.44
% of Control		100.0			998.0			127.0			857.0			148.0	
P Value <		NS			.01			NS			.01			.05	

*Average values for 3 to 5 similar studies done on each patient.

C = Control observations; D = observations after drug administration; I = increase or decrease in function observed; NS = Not statistically significant ($p > 0.10$).

COMMENTS

Pyribenzamine has been shown by the work of Renzi and associates[5] to be a potent diuretic agent in rats; it is comparable to the mercurials. The diuresis induced by antihistaminics in rats was potentiated by preparing the animals with orally administered normal saline. Interestingly enough, the diuretic effect appeared to be independent of antihistaminic activity. Multiple experiments combining hypophysectomies, adrenalectomies, Pitressin, etc., failed to clarify the mechanism by which the diuresis was accomplished. Plummer[6] was able to demonstrate that dogs, infused with saline, were susceptible to Pyribenzamine diuresis, although not with the consistency nor the magnitude found in rats. The data presented in this paper were obtained on dogs which were normally hydrated and demonstrate no significant change in renal hemodynamics and no consistent effects on water and electrolyte excretion.

We were unable to demonstrate a significant and constant diuretic effect of Pyribenzamine in human subjects. However, in a few subjects there appeared to be some tendency toward an increase in water and sodium excretion. The action of a mercurial diuretic, diglucomethoxane (Mersoben), was not significantly altered by Pyribenzamine administration. The explanation for the differences in our studies and those obtained on rats is not apparent.

SUMMARY

1. The effect of Pyribenzamine (tripelennamine) on renal hemodynamics and water and electrolyte excretion for a group of laboratory animals and human subjects are presented.

2. Significant alterations in water and electrolyte excretion could not be demonstrated in dogs.

3. Pyribenzamine did not produce significant changes in renal function or in water and electrolyte excretion when given to human subjects who had either heart failure or the nephrotic syndrome associated with glomerulonephritis.

REFERENCES

1. Bottner, H., and Jueche, K.: Archiv. fur Innere Medizin. **5**:220, 1949.
2. Louvat, M. P.: J. Urol. **56**:295, 1950.
3. Litchfield, H. R., Bressler, N., Mazursky, M., and Greenblatt, J. J.: Am. Pract. & Digest Treat. **4**:104, 1953.
4. Montero, N. O.: Rev. Clin. de São Paulo **27**:119, 1951.
5. Renzi, A., Gilman, M., Gaunt, R.: Fed. Proc. **13**:117, 1954.
6. Plummer, A.: Personal Communication.
7. Moyer, J. H., and Handley, C. A.: J. Pharmacol. & Exper. Therap. **113**:383, 1955.
8. Moyer, J. H., and Mills, L. C.: J. Clin. Invest. **32**:172. 1953.

SOME CIRCULATORY EFFECTS OF MORPHINE-BARBITURATE ANESTHESIA, ARTIFICIAL RESPIRATION, AND ABDOMINAL COMPRESSION BASED ON BALLISTOCARDIOGRAPHIC OBSERVATIONS ON DOGS

With a Review of Pertinent Literature

Wm. R. Scarborough, M.D.*

Baltimore, Md.

INTRODUCTION

THE purpose of this communication is to report certain circulatory alterations which were consistently observed in dogs during morphine-barbiturate anesthesia. These effects were first discovered during experiments which were designed primarily to obtain detailed physical and physiologic data bearing on the origin and significance of the ballistocardiogram.

Although extensive clinical studies using ballistocardiographic methods have been carried out on human beings, the results have provided only limited and indirect information with respect to the relation of these records to cardiovascular function. New improved instruments, termed ultra-low frequency ballistocardiographs, have recently been introduced, and these make it possible to record with greater fidelity over a broader frequency range motions of the human body resulting from the periodic motions of the internal cardiovascular mass. These new instruments are now being systematically applied to the study of human subjects and will doubtless yield better correlations between the ballistocardiogram and the state of the circulatory system than did the older methods. These correlations have been, and will remain, indirect because of the difficulty in measuring in human beings the basic aspects of mechanical circulatory function. The kinds of measurements which may be used in human subjects supply only limited information on over-all cardiovascular function, and hence are insufficient for determining the physiologic significance of ballistocardiographic information. Since circulatory function may be more readily measured and controlled in animals, physiologic work on them was undertaken. Although there were morphologic objections to the dog as an experimental animal, practical considerations made their use a necessity.

From the Johns Hopkins Medical School and Hospital, Baltimore, Md. The views expressed here represent those of a group which includes Drs. B. M. Baker, Jr., S. A. Talbot, F. W. Davis, Jr., M. L. Singewald, R. E. Mason, and E. E. Folk, III.

This work was supported by a Research Grant (H-327) from the National Heart Institute of the National Institutes of Health, U. S. P. H. S., and by a Research Grant (No. G-56-13) from the Life Insurance Medical Research Fund.

Received for publication June 4, 1957.

*Investigator, Howard Hughes Medical Institute.

Ballistocardiographic studies on the dog thus far have been quite limited. In a report in 1945, Hamilton[1] showed a tracing from a dog obtained with a high-frequency ballistocardiographic system of the Starr type; this record was considerably different from those from human beings. Cossio and associates,[2] Frederick, Thomas and associates,[3-5] and Darby and associates[6] have obtained dog ballistocardiograms using modifications of the Dock "direct-body" instruments. The only report thus far on the use of the new ultra-low frequency ballistocardiographic methods in dogs was a recent one by Honig and Tenney.[7]

An ultra-low frequency ballistocardiograph for dogs was designed, fabricated, and subjected to rigorous mechanical testing in this laboratory. Other electromechanical instruments needed for this work were fabricated and put into use. Systematic studies on dogs have been in progress in this laboratory for the past 2 years.

From the outset it was evident that the ballistocardiograms from our anesthetized dogs were variable and inconsistent in wave form. The nature of these alterations and the frequency with which they occurred led us to suspect that they were secondary to circulatory changes produced by anesthesia. It has not been possible to carry out our studies on unanesthetized animals and, since anesthesia was but one of several possible sources of variability, an investigation was begun to try to identify and, to eliminate, if possible, the sources of variability. The results of this study will be presented and their implications discussed.

METHODS

Ballistocardiograph.—The ballistocardiograph consists of a bed or platform of v-shaped cross section made of aircraft honeycomb ("Aircomb") reinforced for rigidity and suspended from above on 4 vertical wires about 1 M. long. A horizontal flexural member attached to the foot of the bed permits head-foot motion, but prevents lateral (side-to-side) motion at this end while it allows unrestricted lateral motion at the other end. In some cases a second member was used at the head to eliminate all lateral motion. Silicone-filled dampers at either end allow adjustable damping in both head-foot and lateral direction.

Seismic reference accelerometers (crystal and Statham strain gauge) were used, one at the foot for head-foot motion and one at the head for lateral motions. The natural frequencies of these transducers are about 70 to 90 cycles per second (c./s.), but because of the presence of variable mechanical and electrical noise, high-cut filters with "corner" frequencies of 20, 30, 40, or 50 c./s. were usually employed.

The over-all weight of the dog bed including dampers, transducers, and devices used to couple the dog tightly to the bed is about 7 pounds. In the head-foot direction the natural frequency is 0.5 c./s. and damping is 25 per cent of critical with a dead weight load of 30 pounds. Frequency response characteristics in the head-foot direction* for the whole system (including bed loaded with dead weight, accelerometers, amplifiers, and recorders) was determined with a variable speed shaker.[8] Without high-cut filters the response of the whole system was found to be reasonably flat over the frequency range from 1 to 35 c./s., with less than 30 per cent amplitude error and less than 20 degrees phase shift. With high-cut filters, for any given corner frequency, f_c, amplitude is down to 50 per cent, and phase lag is 90 degrees at that frequency.

Respiration.—A tracheal cannula with inflatable balloon was used in all experiments. During normal respiration the end was open to the atmosphere and respiration was recorded either from a strain gauge belt about the chest or from an esophageal balloon. Artificial respiration was carried

*Frequency response characteristics for the system in the lateral direction are not given; the data to be presented will be concerned with head-foot records only.

out with the respirator described by Hanlon and co-workers[9] (intermittent positive pressure type) and was modified to give a pressure curve with a smooth gradual inflation phase, a more rapid early deflation phase, and a prolonged post-deflation pause; durations of the inflation, deflation, and post-deflation pause phases were 44, 18, and 38 per cent of the total cycle length, respectively. Respiratory rate and inflation pressure are adjustable; rates of 10 to 18 per minute and maximum inflation pressures of 12 mm. Hg or less were usually employed. Respirator air pressure was recorded with a Statham manometer. Oxygen was used in the earlier experiments, but in more recent ones, only air was used. The respirator was connected to the tracheal cannula with flexible tubing in such a way that there was no restriction of motion or spurious vibration of the dog bed. In some experiments pressures were recorded in the esophagus and stomach with balloon cannulae.

Lead II electrocardiograms and in most cases phonocardiograms were recorded. Intracardiac and intravascular pressures were recorded in some experiments through needles or catheters with Statham and Lilly fluid manometers; zero reference was set midway between back and sternum.

Direct-writer (Sanborn) and photographic (6 channel Hathaway) recorders were used with paper speeds of 2.5 and/or 5.0 cm./sec. A cathode-ray oscilloscope was used to monitor the various physiologic variables during the experiments.

Initial anesthesia consisted of intramuscular morphine (3-4 mg./Kg.) plus either intravenous or intraperitoneal pentobarbital (10-25 mg./Kg.) or dial urethane* and pentobarbital in equal parts (0.25 c.c./Kg.). Small maintenance doses of these agents were given as needed, but anesthesia was kept as light as possible. The total anesthetic dosage for each dog is shown in Table I.

NATURE OF THE NORMAL DOG BALLISTOCARDIOGRAM

It is not our purpose to describe in detail here the characteristics of the normal ballistocardiogram (BCG) obtained from dogs, but rather to indicate the general nature of the normal dog record so as to make more comprehensible the observations to be presented.

In general, normal dog acceleration ballistocardiograms, obtained with ultra-low frequency (ULF) systems, are similar to those from human beings. In Fig. 1 are shown the records from a 10-year-old child and a normal dog. The main systolic and diastolic waves of the human BCG are represented in the dog record. However, a "K wave" is frequently seen in records from dogs, but is characteristically small or absent in human records from ULF systems. The major waves are similar in amplitude and direction in the two records, but there are some differences in timing which may be related to differences in cycle lengths. In Fig. 2 the normal ballistocardiograms from 4 different dogs are shown to illustrate individual differences in wave form. A useful key to wave identity is the time interval between the Q waves of the ECG and the deep negative I of the BCG; the tip of the latter usually falls 0.10 to 0.15 second after the Q wave. Once the I wave is identified the other waves can usually be labeled with ease.

One of the major differences between normal ballistocardiograms from unanesthetized human beings and anesthetized dogs appears to be in the variation in the amplitude of the BCG during normal respiration. Fig. 3,*A* shows the characteristic increase in amplitude during inspiration and the decrease during expiration, in a human subject. This variation in ballistic amplitude is consistent with known changes in outputs of the right and left heart and in total cardiac output during the respiratory cycle.[10-12] However, respiratory variation in amplitude is paradoxical in the dog, as Fig. 3,*B* and *C* shows, in that the largest

*Obtained through the courtesy of Dr. John C. Saunders of the Ciba Co., Summit, N. J.

TABLE I

DOG NO.	EXPERIMENT NO.	DURATION OF EXPERIMENT	MS	BARBITURATE		ROUTE	RESPIRATION		ABDOMINAL COMPRESSION	GENERAL RESULT OF EXPERIMENT	EARLIEST BCGs WITH NR		BCG CHANGES WITH TIME	HEART RATE	
			MG./KG. TOTAL	PENTO MG./KG.	DUP C.C./KG.		NR	AR			AC	FORM	FORM	RANGE	COMMENTS
33	1	8:05	7.70	48.0	—	IV; IP	x	x	Off & on	T(V)	No	N	A	103–37	Decreased with time
	2	8:25	3.13	50.3	—	IV; IP	x	x	Off & on	T	No	N	N(2½ hr.)	82–40	Decreased with time; 40-75 for 4-8 hr. p̄ 1 dose of MS
	3	6:30	3.20	28.8	—	IP	x	x	A.E.& M.	T	Yes	N	N(with AC)	73–33	Decreased with time; decreased with AC and AR
	4	9:00	4.00	29.0	—	IP	x		A.E. & M.	T	Yes	N	N(with AC)	84–48	84 p̄ Pento only; 48-68 p̄ MS
24	5	10:00	7.00	—	0.55	IP	x	x	Off & on	T	No	N	A	43–100	Tendency toward increase with time
	6	5:56	5.80	24.2	—	IP	x	x	Off & on	T	No	N	A	43–67	Slight increase with time; highest with AR and AC
	7	9:15	9.60	52.6	—	IP	x	x	Off & on	T	No	B	A	48–73	Slight increase with time
23	4	10:27	8.80	8.8	0.42	IP	x	x	Off & on	T(V)	No	B	A	107–85	Decreased with time
	5	8:10	4.40	31.0	—	IP	x	x	Off & on	T	No	A	A	87–43	Decreased with time
	6	4:40	2.20	26.7	—	IP	x	x	Off & on	T	No	A	A	100–55	Decreased with time
29	1	7:48	4.40	49.5	—	IV; IP	x	x	Off & on	At.	No	N	N	118–81	Highest with AR and AC
	2	5:10	3.30	39.6	—	IV; IP	x	x	Off & on	T	No	A	A	139–85	Lowest with AR and AC
25	3	6:25	9.20	—	0.35	IP	x	x	Off & on	At.	No	N	A	90–43	Lower with AR (43-72) than with NR (73-90)
	4	5:10	6.60	—	0.37	IP	x	x	Off & on	T	No	B	A	60–70	
36	1	7:15	6.10	34.0	—	IP	x	x	A.E. & M.	At.	Yes	N	A	176–50	176 p̄ Pento only; decreased to 50-60 p̄ MS
28	3	8:10	12.20	—	0.61	IV	x	x	Off & on	T	No	N	N(2 hr.)	161–125	Slight decrease with time
22	4	9:50	6.80	30.0	—	IP	x	x	Off & on	T	No	A	A	33–48	
17	1	7:30	12.20	—	0.41	IV	x	x	Off & on	T	No	B	A	88–58	

Pento = pentobarbital; DUP = dial urethane and pentobarbital; MS = morphine sulfate; IV = intravenous; IP = intraperitoneal; NR = normal respiration; AR = artificial respiration; A. E. & M. = applied early and maintained; T = typical; T(V) = typical, but slightly variable; At. = atypical; N = normal; B = borderline; A = abnormal; AC = abdominal compression.

complexes are during the apneic phase, while the smallest occur during inspiration. There is no definite explanation for this phenomenon at present.

It became clear early in our ballistocardiographic work on dogs that their records were rather unstable, and often showed striking changes in wave form for no apparent reason. Frequently, the earliest control records obtained were

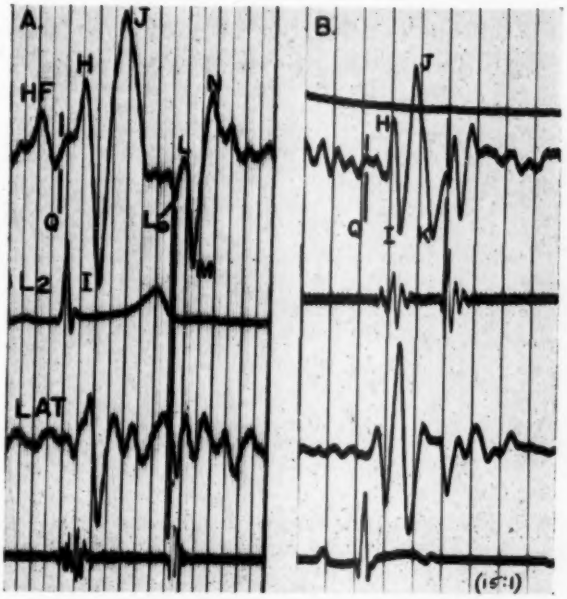


Fig. 1.—Comparison of normal BCG from a human being and a dog. Single head-foot (*HF*) complexes along with ECG, phono, and lateral BCG complexes (*Lat*). In this and all the rest of the figures, unless otherwise stated, heavy time lines are 0.1 second apart. The dark vertical line marked *Q* has been drawn in to make easier the comparison of time relations between the Q wave of the ECG and the ballistic waves. *A*, From a 10-year-old girl weighing 87 pounds. *B*, From a dog weighing 32 pounds. In both records the major waves are similar in amplitude and direction and they occupy the same relative positions in the cardiac cycle, although the absolute duration of systole is considerably less in the dog. The wave marked L_o in record *A* marks the end of systole and its counterpart is present in record *B* also.

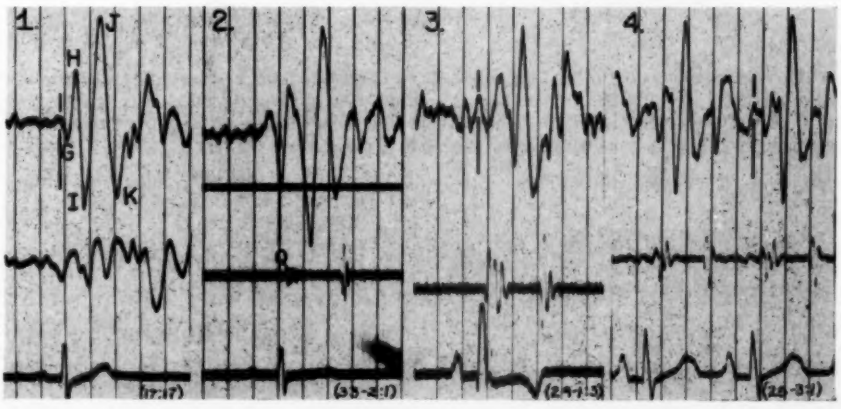


Fig. 2.—Single normal BCG complexes from 4 dogs to show individual differences. In each record the I wave is the deep, negative wave with its tip 0.10 to 0.15 second after the Q wave.

Pento = pentobarbital; DUP = dial urethane and pentobarbital; MS = morphine sulfate; IV = intravenous; IP = intraperitoneal; NR = normal respiration; AR = artificial respiration; A. E. & M. = applied early and maintained; T = typical; T(V) = typical, but slightly variable; At. = atypical; N = normal; B = borderline; A = abnormal; AC = abdominal compression.

normal, but became abnormal later, often after other physiologic procedures were begun and to which the changes in the BCG could possibly be ascribed. This is illustrated by the records in Fig. 4. Tracing 1 was the first BCG obtained and it is normal. Record 2 was taken only 10 minutes later, but already shows some deterioration of wave form. Record 3 was taken after aortic and right heart catheterization and is clearly abnormal. Changes of this kind occurred with such regularity that a thorough exploration of possible sources of variability was initiated, beginning with the following series of experiments.

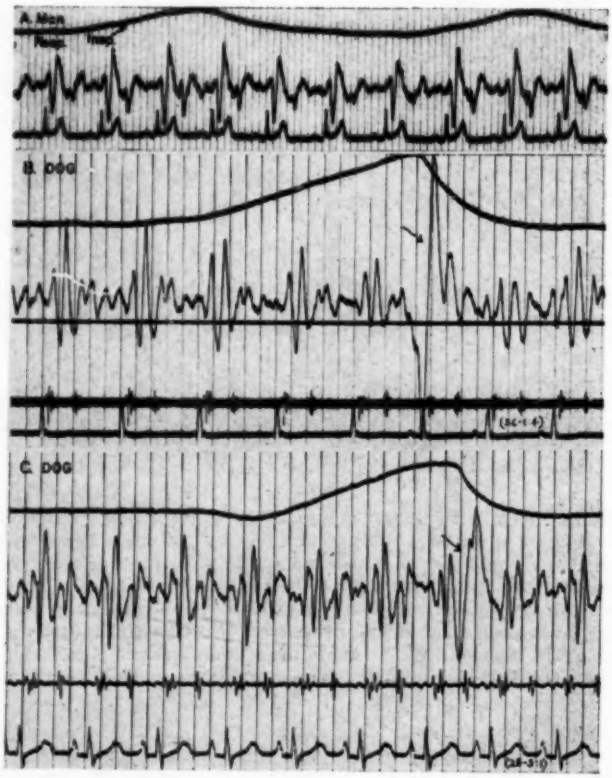


Fig. 3.—Respiratory variation in the amplitude of the BCG from a man (*A*) and from dogs (*B* and *C*). An upstroke of the respiration curve (*Resp.*) indicates inspiration in all three. Paper speed in *A* is half that in *B* and *C*, but heavy time lines are 0.1 second apart in each. In man the amplitude of the BCG increases during inspiration, whereas in the dogs it decreases.

RESPIRATION, BODY POSITION, AND CONSTRAINT EXPERIMENTS

A. *Procedure.*—A total of 15 experiments were carried out on 6 dogs to evaluate the effect on the dog's BCG of several variables including type of respiration, dog's position on the bed, and degree of constraint (loose or tight coupling) of dog to bed.*

*Serial electrocardiograms (standard limb and precordial) were also recorded but these will not be reported on here.

During a single experiment records were obtained with the dog in 6 different positions on the bed: supine (back down), prone, left lateral (left side down), right lateral, left posterolateral (midway between left lateral and supine), and right posterolateral. In each position records were obtained during normal breathing and artificial respiration and with and without constraints (loose or tight coupling, the latter produced with special clamps, ropes for binding legs, and with tape). After completing a run through all positions, this was repeated one or more times later in the experiment. In addition, experiments were run on a number of the dogs on several different occasions.

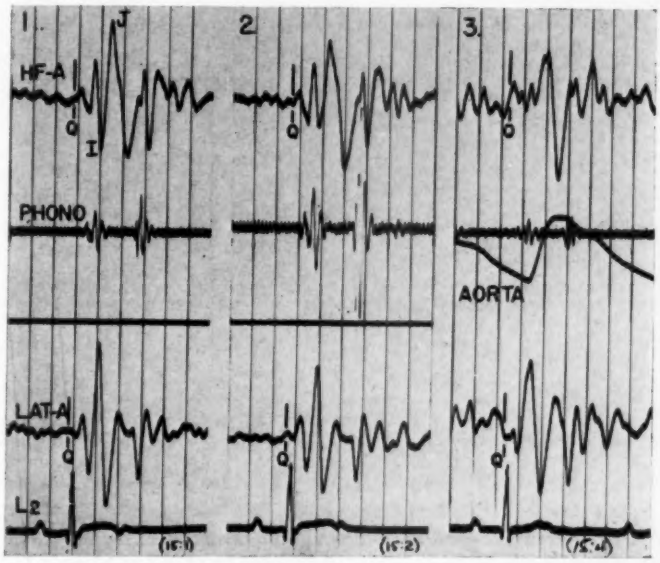


Fig. 4.—Deterioration of a dog's BCG with time. *1*, **First record obtained. Head-foot BCG (*HF-A*) normal. The lateral BCG (*Lat-A*) which appears in this and several other illustrations is to be ignored, since only the head-foot record will be concerned in this paper.** *2*, **Ten minutes later. BCG has begun to deteriorate; amplitudes of I and J waves are reduced and the K wave is relatively deep.** *3*, **After aortic and right heart catheterization. BCG is now quite abnormal.**

B. *Results.*—The records shown in Fig. 5 are rather typical of those from all experiments. The ballistocardiograms taken with the animal in different positions bear little resemblance to each other in wave form, and most are abnormal. In addition, tracings taken in the same position, but at different times, did not resemble each other. The results may be summarized as follows:

The BCG records in this series of dog experiments were characterized by extreme variability in wave form. There was little similarity of the records from the same dog in different body positions under the same conditions of constraint and respiration; there was little similarity of wave form in records obtained under the same conditions (position, constraints, and respiration) but at different times from the same dog; the same was true when a given dog was studied on different days.

Constraints.—With constraints, records appeared to contain somewhat more high-frequency detail than those obtained without constraints.

Position.—There was a slight tendency for records in the prone position to be more normal than in the other positions.

Respiration.—Records obtained during artificial respiration were generally smaller in amplitude and more abnormal in wave form than when the dog was allowed to breathe normally. The sinus arrhythmia and respiratory impacts associated with normal respiration were reduced or eliminated by artificial respiration.

Duration of Experiment.—There appeared to be a definite correlation between the duration of the experiment and abnormality of the wave form, the records obtained late in the experiment being more abnormal than those obtained earlier.

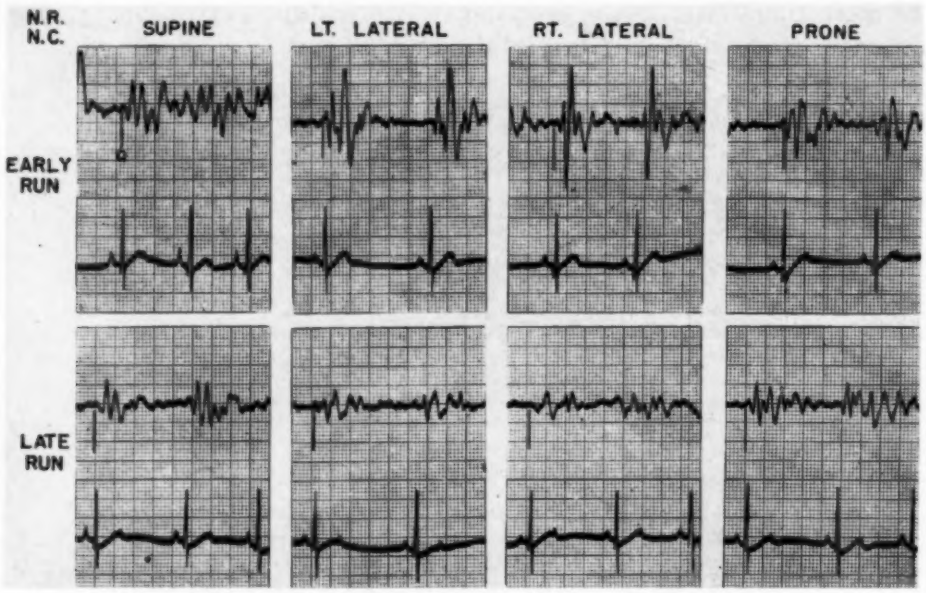


Fig. 5.—Ballistocardiograms from dog in different positions at different times. Heavy time lines are 0.2 second apart. This illustrates the variability in wave form from one position to another, and the differences in pattern in the same position, but at different times. The lower records were obtained about 2½ hours later than those above and are smaller and more abnormal.

These experiments demonstrated clearly the marked variability of the BCG from the anesthetized dog, but did not provide any definite evidence regarding the cause of the inconsistency. However, an experiment of another type did provide a lead as to the factors responsible and also suggested a means of nullifying them. The first part of this experiment was similar to those described above and yielded the same variability of BCG wave form observed in the others. Fig. 6,*A* shows the abnormal record taken at the end of this part of the experiment to serve as a control for the second part. This latter was designed to furnish information on certain circulatory effects of abdominal compression, because it was known that in human beings abnormal ballistocardiograms were frequently improved by the application of an abdominal binder. After making record *A* of Fig. 6 the right heart was catheterized (double lumen catheter), a balloon-cannula was inserted to permit the recording of gastric and esophageal pressures, and an abdominal binder was applied, but the pneumatic cuff was not inflated. Record *B* was then recorded and this showed striking improvement in the BCG, which is essentially normal. In record *C*, taken a few minutes later after retraction of the cardiac catheter, amplitude has fallen and wave form has changed

somewhat. Record *A* of Fig. 7, taken still later, shows a further tendency toward deterioration. Record *B* was taken during abdominal compression and it shows reversion to a normal wave form and increase in amplitude. Record *C* was taken 20 seconds after the release of compression and it shows a return to the control

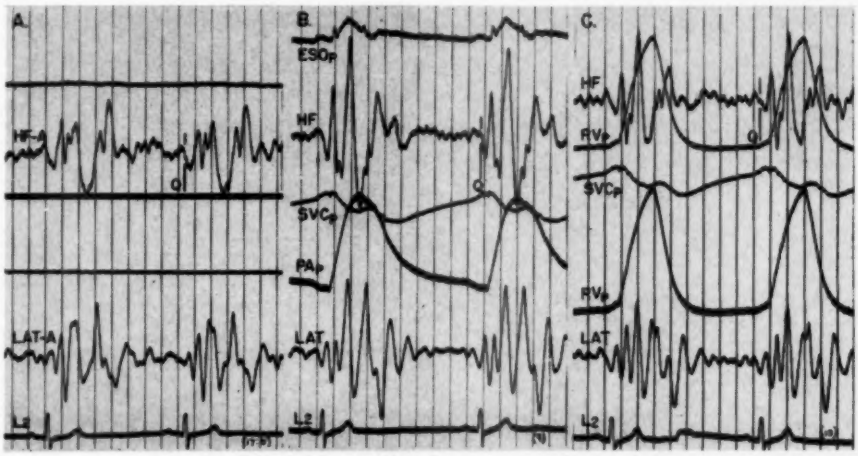


Fig. 6.—Effect of applying a binder snugly around dog's abdomen. *A*, Control BCG grossly abnormal. *B*, Record after right heart catheterization, insertion of gastric and esophageal balloon cannulae, and after placing binder about the abdomen with inflatable cuff beneath it. Record was taken before the pneumatic cuff was inflated but the binder was undoubtedly producing some abdominal compression. From above down, esophageal (ESO_p), head-foot BCG (*HF*), superior vena caval (SVC_p), and pulmonary artery (PA_p) pressures; lateral BCG (*Lat*) and ECG. The BCG shows greatly increased amplitude and normal wave form. *C*, Record taken a few minutes later after retracting catheter tip from the pulmonary artery to the right ventricle. There are two right ventricular pressure curves (RV_p); the upper one should be ignored. The amplitude of the BCG has decreased and wave form has changed.

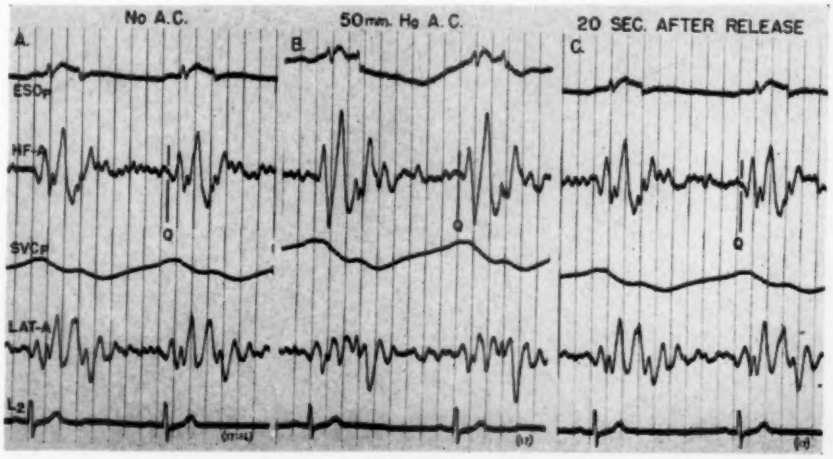


Fig. 7.—Effect of abdominal compression (*A.C.*) from same experiment as Fig. 6. *A*, Control record taken somewhat later than record *C* of Fig. 6. Further reduction of the BCG amplitude; wave form not normal. *B*, During inflation of pneumatic cuff beneath abdominal binder. Amplitude of the BCG considerably increased and wave form distinctly improved. Note the small increase in esophageal and SVC pressure. *C*, Twenty seconds after release of abdominal compression the BCG has reverted to wave form and size of the control, and intrathoracic pressures have also fallen.

wave form. This procedure was repeated a number of times during the experiment, and in each case the use of abdominal compression was associated with distinct improvement in the BCG. Record *B* in Fig. 6 was obtained immediately after the binder was applied, but before it was inflated; presumably this provided enough compression to render the BCG normal, but did not produce a sustained effect.

The results of a few additional pilot experiments yielded similar results. A systematic investigation was begun of the effects of respiration (normal and artificial), abdominal compression, and barbiturate anesthesia on the dog's BCG. Much of the work to be described was concerned with the consistency of results, and in order to minimize the number of experimental variables, the procedures were kept as simple as possible.

ANESTHESIA, RESPIRATION, AND ABDOMINAL COMPRESSION EXPERIMENTS

A. *Procedure.*—Twenty-one experiments were carried out on 12 normal dogs; 3 experiments on 3 dogs are excluded because they were technically unsatisfactory (defective respirator and/or overdamped, dragging dog bed) and, therefore, only the 18 satisfactory experiments on 9 dogs are included in the analysis. Abdominal compression was produced in two different ways. In some cases a girdle-like canvas binder was secured snugly in place with straps about the dog's body. In others a folded blood pressure cuff was placed beneath the binder and inflated with air (20 to 30 mm. Hg).

In most experiments (15 of the 18) abdominal compression was not applied until after a number of control observations had been made over a period up to 3 hours after anesthesia. Records were taken repeatedly during normal or artificial respiration, both with and without abdominal compression. In a few experiments, abdominal compression was applied shortly after anesthesia and was maintained throughout most of the experiment.

In a few instances, the effect of tilting the animals, head upward or downward, was tested, but these data are too limited to be reported until more have been accumulated.

The weights of the dogs, duration of the experiments, anesthetic dosage, and other data are contained in Tables I and II. The number of experiments on each dog ranged from 1 to 4.

B. *Results.*—

1. *Effects of respiration and abdominal compression on the BCG:* The results in this series of experiments were generally consistent. In "typical" experiments, the ballistocardiograms recorded during the initial "normal respiration/no abdominal compression" period were either abnormal at the outset or showed gradual deterioration with time. The use of artificial respiration without abdominal compression led to further deterioration of wave form and decrease in amplitude. However, when abdominal compression was then applied and maintained, the BCG wave form became normal, or nearly so in most of the cases. The over-all results from each experiment were classified as "typical" if they fit this pattern,

or as "atypical" if they did not, and are shown in Table I under "General Results." In 15 of the 18 experiments the results were typical and in only 3 were they atypical or variable. Figs. 8 to 10 exemplify the findings in most of the experiments. Fig. 8 shows the sequence of events which occurred in a typical experiment. In the record obtained early in the experiment with the dog breathing normally and with no abdominal compression, the BCG was normal. Under the same conditions, but 30 minutes later, the record had become abnormal and showed further deterioration during artificial respiration. With maintained artificial respiration, abdominal compression was applied and the BCG became normal. Releasing abdominal compression and allowing normal respiration, the wave form deteriorated and the record became abnormal. With continued normal respiration and after reapplication of the abdominal binder, the BCG returned to normality. In Fig. 9 the first record obtained was grossly abnormal. Abdominal

TABLE II. 18 EXPERIMENTS ON 9 DOGS

1. Dog Weights:
   Mean of 9 = 25.8 pounds or 11.7 kilograms
   Range of 18 = 40 pounds or 8.2 to 18.2 kilograms
2. Duration of Experiment:
   Mean = 7 hr. and 40 min.
   Range = 4 hr. and 40 min. to 10 hr. and 27 min.
3. Anesthesia:
   a. Morphine sulfate in mg./Kg.: Mean of 18 = 6.48 mg./Kg.; range = 2.2 to 12.2 mg./Kg.
   b. Pentobarbital in mg./Kg.: Mean of 12 = 37.0 mg./Kg.; range = 24.2 to 52.6 mg./Kg.
   c. DUP (dial urethane and pentobarbital) in c.c./Kg.: Mean 5 = 0.46 c.c./Kg.; range = 0.35 to 0.61 c.c./Kg.
   d. DUP and pentobarbital in 1 case: DUP = 0.42 c.c./Kg. and pentobarbital = 8.8 mg./Kg.
4. Types of Respiration:
   a. Both normal and artificial respiration in 17 of 18 experiments
   b. Normal respiration only in 1 of 18 experiments (No. 33-4)
5. Abdominal Compression:
   a. Off and on in 15 of 18 experiments
   b. Applied early and maintained in 3 of 18 (Nos. 33-3; 33-4; 36-1)
6. Earliest BCG Records and Changes with Time:
   a. With normal respiration and no abdominal compression (15 experiments)
      1. Initial BCG normal in 7; remained normal in 3; became abnormal in 4
      2. Initial BCG borderline in 4; became abnormal in all 4
      3. Initial BCG abnormal in 4; remained abnormal in all 4
      4. BCG became or remained normal in 3; borderline in 0; abnormal in 12
   b. With normal respiration; abdominal compression applied early and maintained (3 experiments)
      In 2 of these morphine sulfate was given later than pentobarbital, and in each case the BCG before morphine sulfate was abnormal or borderline, but became normal after morphine sulfate. One remained normal with abdominal compression, and the other later became abnormal with abdominal compression maintained. In 1 the earliest BCG was normal and remained normal with maintained abdominal compression
7. General Result of Respiration and Abdominal Compression Study (See Text):
   a. Typical result in 15 of 18
   b. Unusual, variable, or atypical result in 3 of 18 (Nos. 29-1; 25-3; 36-1)

compression was then applied and the BCG became normal. After releasing the abdominal compression and starting artificial respiration, the record again become abnormal. Finally, while maintaining artificial respiration, abdominal compression was reapplied and the BCG returned to normal once more. Fig. 10 shows similar improvement in wave form associated with the use of abdominal compression during both normal and artificial respiration.

The striking tendency toward early deterioration of the BCG was evident from serial records obtained during an initial normal respiration period before

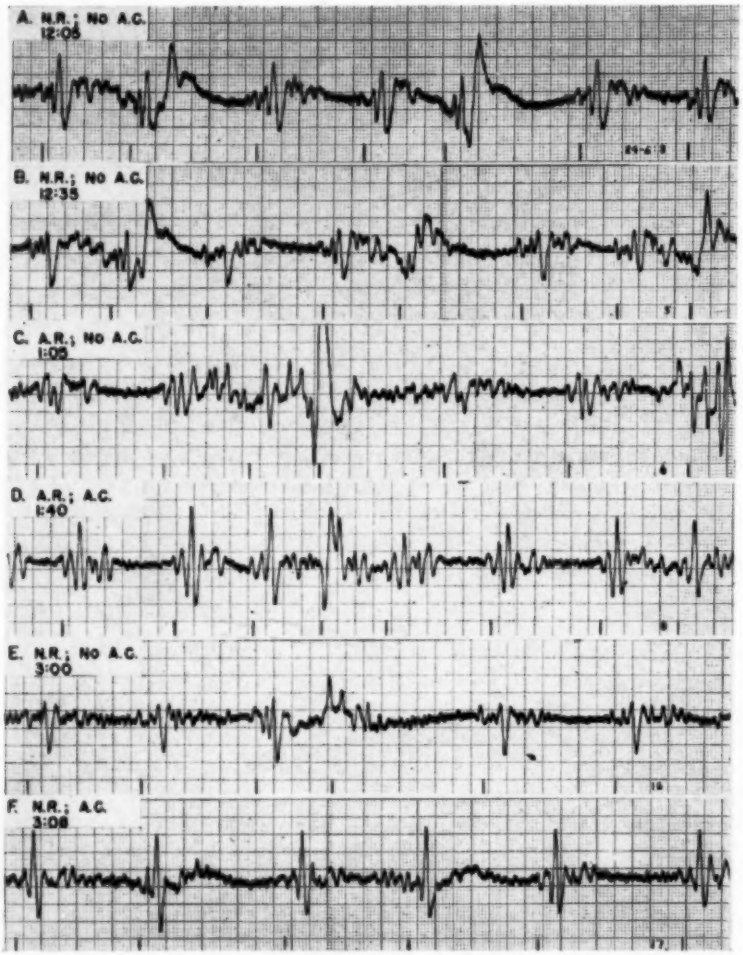


Fig. 8.—Sequence of events in one experiment showing effects of time, respiration, and abdominal compression. *N.R.* and *A.R.* refer to normal and artificial respiration, respectively. *A.C.* refers to abdominal compression. Time of day is shown in the upper left corners. Heavy time lines are 0.2 second apart. The large deflections which occur periodically are artefacts created by respiratory impacts. The small vertical lines which are below and precede the BCG complexes mark the onset of the QRS complex of the simultaneously recorded ECG. These tracings were retouched for purposes of reproduction. *A*, Record obtained early in experiment. BCG is normal. *B*, Thirty minutes later. BCG has spontaneously deteriorated and complexes are small and abnormal. *C*, Thirty minutes later and during A.R. BCG more abnormal. *D*, During A.R. and after application of A.C. BCG shows striking improvement in wave form and amplitude and is now normal. *E*, During N.R. and no A.C. BCG has again become grossly abnormal. *F*, Eight minutes later and after re-application of A.C. BCG has reverted to normal.

abdominal compression was applied. In 12 of 15 such experiments, the BCG was either abnormal in the first record or became abnormal later. In only 3 did wave form remain normal for the first 2 to 3 hours of the experiment (See Tables I and II).

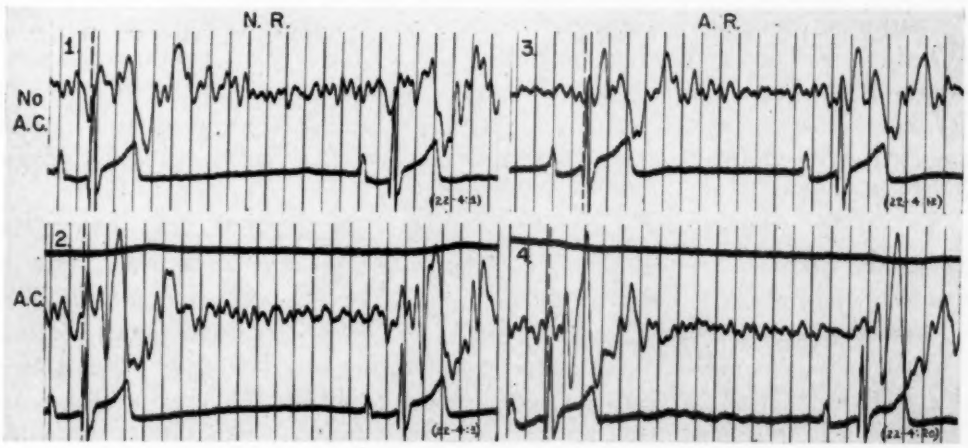


Fig. 9.—Effect of respiration and abdominal compression. Records 1 through 4 are from the same experiment and are in proper time sequence: 1 and 2 during normal breathing, 3 and 4 during A.R; 1 and 3 without A.C., 2 and 4 with A.C. The initial record, 1, is grossly abnormal, but becomes normal with A.C. The same effect occurs later during A.R.

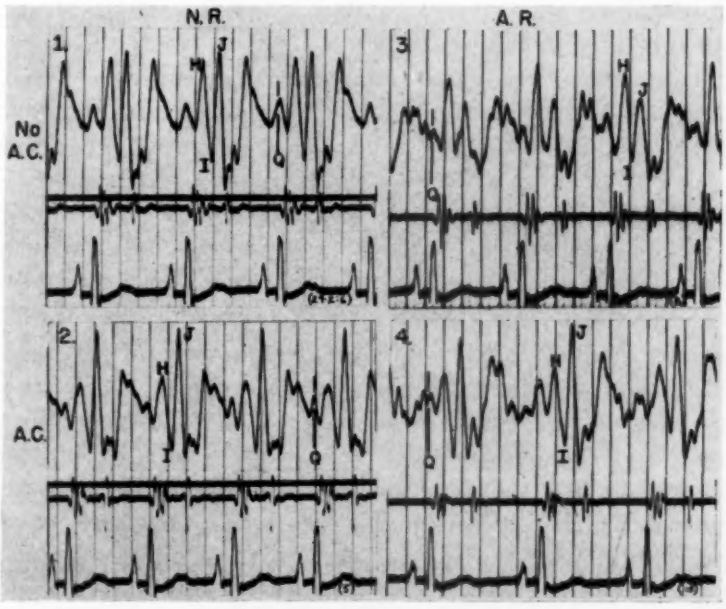


Fig. 10.—Effect of respiration and abdominal compression. Another dog and experiment. Record 1 is not so grossly abnormal as its counterpart in Fig. 9, but the effects are sim'lar and the BCG is normal during compression of the abdomen, regardless of the type of respiration.

In view of the previously observed marked variability of the BCG from dogs when in different body positions, abdominal compression during several experiments was maintained and the dog's position was varied. The records obtained in the different positions were found to be similar in wave form.

An effort was made to determine how long normal ballistocardiograms could be obtained during normal respiration when abdominal compression was applied early and maintained. In most experiments, whether respiration was normal or artificial, normal ballistocardiograms could be obtained for 6 or more hours when abdominal compression was used. However, in one experiment (No. 33-1) the BCG was abnormal in all records during abdominal compression, but became normal after the compression was removed; it is possible that the pressure applied was excessive in this instance.

2. *Effect of anesthesia on the BCG:* Progressive deterioration of the BCG consistently occurred in the normally breathing dog after anesthesia, and the use of artificial respiration almost invariably increased the degree of abnormality. We have not been able to obtain control observations on unanesthetized dogs, nor was it possible in these experiments to determine or control the level of anesthesia. The variations in duration of experiments, in dosage of anesthetics, and in frequency of administration introduce further analytic difficulties. Our data do not permit a correlation between total anesthesia dosage and the tendency toward ballistocardiographic deterioration.

In most cases the dogs were given morphine before, or with, the barbiturate anesthetic. However, in 2 experiments (Nos. 33-4 and 36-1) morphine was temporarily withheld and records were taken after only the barbiturate was injected. The BCG was borderline in one and abnormal in the other; both became quite normal after morphine was given. A similar effect was observed in another experiment not included in this series.

All of the data presented were obtained from intact, closed-chest dogs. In a few, cut-downs were performed to permit catheterization; most of them were not subjected to any form of surgical trauma and no drugs were given except the morphine-barbiturate anesthetics. For this reason it is difficult to ascribe the ballistocardiographic deterioration to causes other than anesthesia. The marked changes in these records occurred with anesthetic doses which were by no means excessive; on the average, these dogs were given only 6.9 mg./Kg. of morphine and 37 mg./Kg. of pentobarbital over a period of 7 hours and 40 minutes.

3. *Heart rate changes:* (See Table I.) In most experiments heart rates were highest early and declined later to relatively low values. Rates below 60 were not unusual, occurring in 14 of 18 experiments. In contrast to the usual fall in rate with time, in all 3 experiments on one dog (No. 24) the earliest rates were below 50 and rose during the experiment. Morphine was believed responsible for the bradycardia; in fact, it was for this reason that morphine was used. Pulse rates were comparable with the two kinds of barbiturate anesthetics.

Although in some individual experiments the pulse rate appeared to be related to the type of respiration and to the presence or absence of abdominal compression, there was no definite correlation for the whole group. No relation was evident between pulse rate and normality of the ballistocardiographic pattern.

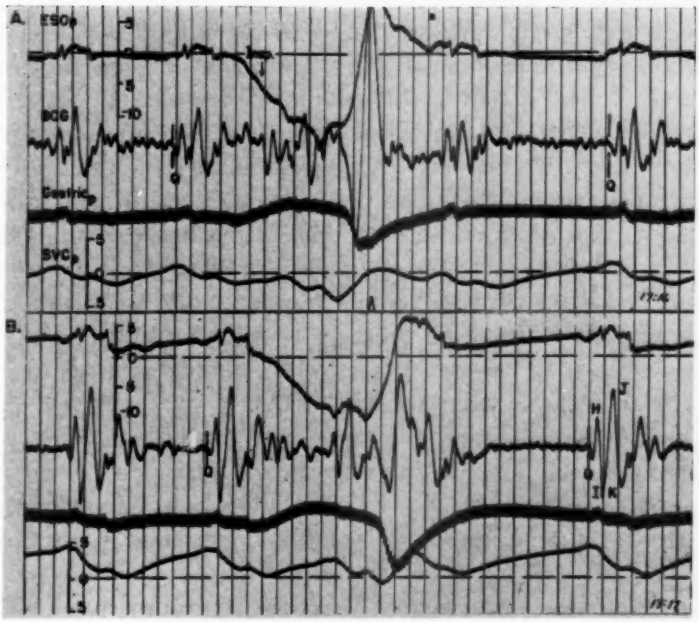


Fig. 11.—Effects of abdominal compression on pressures in the thorax and abdomen during normal respiration. *A*, No compression. *B*, With abdominal compression. In each record, from above downward, the tracings are: esophageal pressure (ESO_p), BCG, gastric pressure, superior vena caval pressure. (All pressures are in mm. Hg.) The broken lines represent 0 pressures. The gastric pressure tracing which contains 60 c./s. electrical noise was obtained with a transducer having a low-frequency cutoff, which made it useful only for measuring phase changes in pressure. On application of compression to the abdomen, there are small increases in esophageal and central venous pressures and there is concomitant improvement in the BCG form and amplitude.

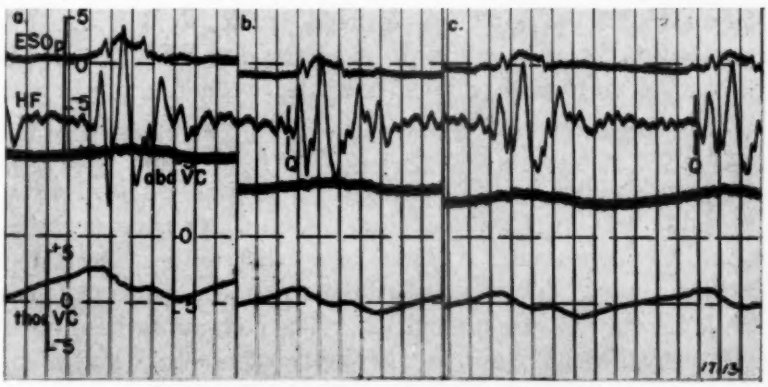


Fig. 12.—Venous pressures in the thorax and abdomen during abdominal compression and after release. From same experiment as records in Fig. 11 and showing same tracings except that abdominal vena caval pressure was recorded instead of gastric pressure. *a*, During compression. *b*, Ten seconds after release. *c*, Twenty seconds after release. All 3 strips were obtained during normal postexpiratory apnea. During compression the BCG complex is normal; after release of the compression there is a prompt reduction in BCG amplitude and a progressive partial deterioration of wave form. This is associated with small decreases in esophageal and central venous pressures and a slightly greater fall in abdominal venous pressure.

4. *Other effects produced by respiration and abdominal compression:* In a few experiments pressures were measured in the abdominal and thoracic vena cava, in the stomach and esophagus (air), and in the right atrium, ventricle, and pulmonary artery. In general, the effects of abdominal compression during normal respiration were: (1) increased air and venous pressures in the abdomen and in the thorax, with relatively greater increases in abdominal pressure and, consequently, an increase in venous pressure gradient from abdomen to chest, (2) improvement of wave form and increased amplitude of ballistic complexes, (3) decreased depth and duration of inspiration (esophageal pressures) and reduced inspiratory fall in central venous pressure, and (4) the reduction of the early expiratory "after-fling" in pressures. The tracings in Figs. 11 and 12 illustrate these effects. These results must be regarded as tentative until more data bearing on them have been accumulated.

During artificial respiration the thoracic and abdominal venae caval pressures were somewhat higher and the respiratory variations in pressures were, of course, no longer reciprocal. However, our limited data suggest that abdominal compression produces an increase in venous pressure gradient during artificial respiration similar to that during normal breathing.

During fluoroscopic observation abdominal compression produced the expected elevation of the diaphragm.

DISCUSSION

Our observations indicate (1) that the ballistocardiograms from supine dogs under morphine-barbiturate anesthesia quite frequently show spontaneous deterioration of wave form which progresses with time, (2) that positive pressure artificial respiration hastens the onset of deterioration and increases the degree of abnormality, and (3) that abdominal compression may prevent or reverse these effects and restore the normal ballistocardiographic wave form. Similar observations on dogs have not been reported previously.

The explanation for the deterioration of the dog BCG has not been clearly established, but the most likely one is that it is a reflection of circulatory alterations induced by morphine-barbiturate anesthesia and by artificial respiration.

The circulatory effects of barbiturate anesthesia have been studied extensively in man and animal, with a variety of methods. The results have been somewhat variable, but on the whole indicate that these drugs produce changes in cardiac output, blood pressure, regional blood distribution, and venous return, depending on the amount and route of administration, the duration of anesthesia, and the functional state of the circulation. The commonly used barbiturates all appear to cause qualitatively similar cardiovascular effects and differ mainly in rapidity and duration of action.[13]

It is probable that barbiturates, if given rapidly in large quantities, are capable of directly depressing the myocardium, but respiratory failure would doubtless appear first unless respiration were maintained artificially. Whether there is a toxic effect on the heart with the doses usually employed is debatable. Cardiac dilatation and failure in animals has been ascribed to barbiturate-induced myocardial depression by several observers,[14-16] but no direct toxic effect could

be found by others.[17,18] In rabbits, Gordh[13] observed marked cardiac dilatation and "reduced reserve" even when moderate doses were used, but it is worth noting that in his animals central venous pressure remained normal in the supine position until respiratory arrest and death were produced. In several recent studies on human beings in which the level of anesthesia was carefully controlled, central venous pressure remained normal and there was no evidence of myocardial insufficiency.[19-21] In an x-ray study of heart volume in human subjects, no cardiac dilatation was observed during barbituric acid anesthesia.[22] The extensive use of the short-acting barbiturates for surgery on human beings in recent years has not disclosed any definite toxic myocardial effect.[23]

It is generally agreed that the important circulatory effects of the barbiturates stem from their depressing influence on vasomotor tone and control. A decrease in arterial blood pressure is one of the cardinal effects, and until recently this was attributed to lowered peripheral resistance due to arteriolar vasodilatation. A variety of studies in human subjects and in animals provided support for this view, but most of these observations were made on localized vessels, vascular beds, or parts of the body rather than on the whole circulatory system. The introduction of reliable cardiac output methods made possible the measurement of pressure, flow, and peripheral resistance for the whole systemic circulation. Recent work[13,19,20,24-27] along these lines has shown rather clearly that during barbiturate anesthesia total peripheral resistance is usually unchanged or increased, while cardiac output is decreased. These findings indicate that the decrease in arterial pressure must be accounted to the reduced output. Since there is no evidence of cardiac insufficiency, it is now held that the reduction in cardiac output stems from decreased venous return as a result of pooling and redistribution of blood. There is a considerable body of evidence, both direct and indirect, to support this view. Johnson,[24] Fieldman and associates,[19] and Etstein and Li[20] recently observed in patients under barbiturate anesthesia a significant decrease in "pulmonary" or "intrathoracic" blood volume which paralleled a decrease in cardiac output. These blood volume calculations, based on dye-dilution curves, do not provide an exact measure of the blood within the thorax, but probably do allow a rough estimate. The decrease in "intrathoracic blood volume," in the absence of a significant change in total blood volume, implies the transfer of blood from the thoracic area to the capacious splanchnic and peripheral vascular beds. There are numerous observations which indicate that increased quantities of blood are contained in these areas during barbiturate anesthesia and this will be commented on later.

The pulmonary blood volume provides a reserve of blood to insure adequate filling and output of the left heart when the output of the right heart is reduced or when there is a lag in increase in venous return following a sudden increase in demand for cardiac output.[28,29] Normally, the volume of blood within the chest constitutes 15-30 per cent of the total blood volume. Sjostrand[30] showed that within this range cardiac output remains relatively constant while stroke volume varies directly and pulse rate inversely with pulmonary blood volume. However, when the latter falls below 15 per cent during barbiturate and spinal anes-

thesia,[24] stroke volume falls more rapidly and is not compensated for by an increase in pulse rate, so that cardiac output falls in a linear fashion with the decrease in pulmonary blood volume.

The over-all circulatory effects of barbiturate anesthesia now appear to be redistribution of blood from the thorax with pooling in other areas, reduced venous return, cardiac output, stroke volume, and arterial pressure, and increased cardiac rate. The magnitude of the circulatory alterations seem to depend on the amount and rate of drug administration; they may last for hours after the anesthetic is stopped.[19] Shore and his co-workers[25] observed in dogs that cardiac output was decreased markedly during the first 4 hours after injection of a single dose of sodium barbital, and similar results have been reported by others.

It seems probable that the progressive reduction in amplitude and deterioration in wave form observed in the ballistocardiograms of anesthetized dogs result from these circulatory effects of barbiturate anesthesia. Acceleration ballistocardiograms from ULF systems of the sort used in this work do not measure stroke volume but rather the force generated in ejecting each stroke volume. Well-filled hearts eject forcefully, but when poorly filled they do not, as we have observed in animals with reduced venous return due to mechanical constriction of the inferior vena cava.[31] Within a few seconds after complete caval occlusion, we have found that the ULF ballistocardiogram virtually disappears, in contrast to results reported by others.[2,4]

The cause of the circulatory alterations produced by barbiturate anesthesia appears to be due to depression of vasomotor control, with partial paralysis of the sympathetic vasoconstrictor mechanism by which the circulation normally compensates for diminished venous return, cardiac output, and arterial blood pressure. This is exemplified by failure to compensate for a variety of "stresses" which are normally well tolerated. Unanesthetized man can withstand the vertical posture, positive pressure artificial respiration, or venesection with but minor circulatory changes,[30,32,33] whereas in anesthetized man and animals these procedures are poorly tolerated and tend to magnify the effects of barbiturates on venous return, output, and pressure.[34,35] Morphine, anoxia, and hypercapnia also enhance these effects.[13,37]

The accumulated evidence suggests that circulatory effects similar to those during barbiturate anesthesia also occur in other conditions wherein the integrity of the reflex vasomotor control system is lost. These include section of the cervical cord,[38] spinal anesthesia,[24,39-41] thoracolumbar sympathectomy,[38,39] ganglionic blocking agents,[44-51] section of the splanchnic nerves,[38] normovolemic shock,[54] and, as a special case, idiopathic postural hypotension.[28] Based on information now at hand, the effects of impaired reflex sympathetic control cannot be blamed on arteriolar vasodilatation, since total peripheral resistance, determined largely by arteriolar resistance, is not significantly reduced. This of course does not deny that arteriolar dilatation in some vascular beds may be compensated for by constriction in others. However, the readiest explanation for an increase in volume or capacity of a given vascular bed, when arteriolar resistance is unchanged, would be a dilatation or decrease in tone of the capillaries and/or veins.

The capillaries are believed to contain only about 10 per cent of the total blood volume, whereas the veins contain about 70 per cent.[59,60] In the low-pressure, high-capacity venous system slight reduction in venous tone and venous pressure gradient could cause the pooling of large quantities of blood. Consequently, reduction in venomotor tone through inhibition of sympathetic control could account for the pooling and redistribution of blood during barbiturate anesthesia and the other related conditions mentioned. The exact role played by venous tone in the regulation of the circulation is still a debated issue, but there is increasing evidence that venomotor tone plays an active part in controlling circulatory capacity similar to that played by arteriolar tone in controlling arterial pressure and flow.[59-74,82-84]

The reservoir function of the splanchnic bed has long been known and its importance in the control of arterial blood pressure has been emphasized.[75,97] Its capacity is large and can be widely varied; normally this area (excluding kidneys) receives about 20 per cent of total cardiac output and contains about 20 per cent of the total blood volume[50,114]; it is probably capable of containing the entire blood volume.[38] The splanchnic vessels are supplied with by far the strongest of the vasoconstrictor nerves. Splanchnic or sympathetic stimulation (direct or reflex) has been shown to produce intense splanchnic vasoconstriction, marked increase in arterial pressure, decrease in the size of liver, spleen, kidneys, and constriction and increase in tone of the intrahepatic vessels of the portal venous tree[61] and of the inferior vena cava[62,63] and mesenteric veins.[64,65] There is also recent evidence that adrenergic stimulation increases venous return and cardiac output.[76,77] On the other hand, cutting the splanchnic nerves produces splanchnic vasodilatation, a marked drop in arterial pressure, and an increase in the size of the abdominal organs. Cholinergic stimulation has been found to dilate and decrease the tone of the abdominal vena cava[63] and, in addition, to reduce venous return and cardiac output.[77] Similar effects have been observed during direct or reflex suppression of sympathetic vasomotor activity.[64,76,80,81] These observations suggest that the splanchnic veins as well as arteries actively participate in the control of the circulation.

A definite reduction in hematocrit is considered characteristic of barbiturate anesthesia in the dog.[55] This hemodilution is believed to be due to the storage of red cells in the spleen, since it does not occur after splenectomy.[56-58] In human beings the spleen is not believed to play an important role in red cell storage, but it is of interest that the characteristic hemodilution observed in dogs is seen also in man during barbiturate anesthesia[20] and during autonomic blockage with hexamethonium.[48,52]

Maintenance of relatively normal amounts of blood within the "pulmonary reservoir" is believed important in meeting the varying demands for cardiac output, but there is no definite proof that the capacity of the pulmonary bed as a whole is under direct neurogenic control.[89,90] There is evidence that the pulmonary blood volume is regulated by sympathetic vasomotor influences on other vascular beds. That the splanchnic bed may be important in this connection is suggested by reciprocal changes in blood volume which have been observed under certain circumstances in the pulmonary and splanchnic beds.[36,53,89,91-95]

The fact that there are reciprocal changes in the blood volume of pulmonary and splanchnic beds does not necessarily mean, of course, that other areas are not involved in this redistribution of blood.

Aside from serving as a reservoir for blood and as an area of variable resistance for controlling arterial blood pressure, the abdomen is also part of the "respiratory pump" which assists in maintaining venous return.[75,98] Brecher and colleagues[34] have done much to clarify the behavior of this pump. It should be recalled that the veins of the thorax and abdomen form a common system unbroken by valves, whereas those outside of this area are broken into segments by venous valves so arranged that backflow of blood is prevented. During inspiration the diaphragm descends like a large piston, aspirating blood into the chest through both cavae and at the same time compressing and milking blood out of the liver and abdominal veins. The increased intra-abdominal pressure retards venous inflow from the lower extremities, but the venous valves prevent reflux, so that blood is temporarily pooled in the veins outside of the abdomen, and venous pressure rises. During expiration the diaphragm ascends, abdominal pressure drops, the blood pooled under pressure in the veins of the lower extremity flows into the abdomen and that pooled in the portal veins flows into the vascular bed of the liver.[34,99] The abdominal veins are then once again refilled and ready for the next cycle. Although active participation of abdominal muscles during quiet breathing is doubted, good abdominal tone would seem necessary for efficient operation of the "respiratory pump" by bracing the abdominal wall so that intra-abdominal tension may increase during inspiration and squeeze blood out.

A number of years ago Kerr[100-105] noted that certain patients with angina pectoris were much improved symptomatically by wearing an elastic abdominal belt. He believed that this enhanced the action of the diaphragm and thereby improved venous return, cardiac output, and coronary blood flow. On assuming the erect posture his patients did not compensate as well as normal individuals, in that systolic and pulse pressure dropped and remained low as long as they stood, but increased after the elastic belt was applied. He also observed that when the belt was worn, circulation time shortened, tidal volume increased, and, on fluoroscopy, diaphragmatic excursion became greater and the systolic excursions of the heart markedly increased in amplitude. There was increase in exercise tolerance in all of his 19 patients when the abdomen was supported. At about the same time Starr[106] tested this effect on the ballistocardiograms of patients with abnormally small complexes; tight compression of the abdomen regularly produced considerable increases in the amplitude of these records. It has become well established that in a high proportion of patients with coronary disease the resting, supine BCG is abnormal,[107-109] and the abnormality is most marked during the expiratory phase of respiration. Along with others, we observed that there was often distinct improvement in the wave form and amplitude of these records on application of abdominal compression and that the improvement persisted as long as compression was maintained.[108] Brown and de Lalla[110] obtained similar results and, in addition, observed symptomatic improvement in patients with angina who regularly wore abdominal supports. In patients

with hypertension they found that following dorsal sympathectomy the BCG became abnormal, or more so, with virtual disappearance of the complexes during expiration. The application of elastic stockings and tight abdominal support produced marked improvement in the record and, incidentally, eliminated postural syncope. A few of these patients after sympathectomy developed precordial pain resembling angina while standing and this could be relieved by abdominal compression, mild exertion, or lying down.

Normally the outputs of the right and left hearts fluctuate in a reciprocal fashion during the respiratory cycle, but the combined output of both ventricles increases during inspiration and decreases during expiration.[10-12] The amplitude of the complexes in the normal human BCG varies in the same fashion as does total output during respiration.[88,96] The respiratory variation in right ventricular output is much greater than that of the left, so that during inspiration the increase in the output of the right heart considerably exceeds the decrease in the output of the left, and the excess blood pumped by the right ventricle is temporarily stored in the pulmonary bed. During expiration the pressure gradient favors the return of this stored blood to the left heart, so that its filling and output are increased while those of the right heart are decreased.

Brown and deLalla suggested that in postsympathectomy patients, and perhaps in patients with angina pectoris as well, there might be pooling of blood in the splanchnic and peripheral beds leading to a decrease in venous return and a reduction in pulmonary blood volume to such an extent that the pulmonary pool is no longer large enough to adequately maintain left ventricular filling and output during expiration. This seemed a reasonable explanation for the small and abnormal ballistocardiographic complexes during expiration, since the amplitude during this phase depends mainly on left ventricular output. The improvement in the BCG with abdominal compression was attributed to reduction of splanchnic pooling, improved venous return, and increased pulmonary pool which in turn enhanced left ventricular filling and output. McCann[111] apparently shared this opinion.

Improvement of abnormal ballistocardiograms with abdominal compression was noted not only in our patients with coronary disease, but also in older, presumably normal persons with abnormal control records.[112] However, it was not clear exactly what physiologic effects were produced in human beings by abdominal compression, and therefore during an experiment on an anesthetized dog we sought an answer to this question.

As we have reported, our earlier experience with ballistocardiograms obtained from anesthetized dogs revealed a rather marked variability in wave form, and if they were not abnormal at the outset, they became so during the period of observation. However, the fact that some records early in the experiments were quite similar to normal human records, and then became abnormal with time, suggested that some progressive change in circulatory function was taking place. The fortuitous and surprising observation that the abnormal BCG from an anesthetized dog became normal with abdominal compression led us to the investigation now being reported. This observation was confirmed numerous times and in most cases normal records could be obtained for many hours by using this

expedient. Our working hypothesis was that barbiturate anesthesia caused pooling of blood in the splanchnic area, with reduction in venous return and cardiac output. Strapping the animal down in an unmoving position for several hours, with the loss of muscle tone, would tend to enhance these effects. Intermittent positive pressure artificial respiration usually produced marked abnormality rather rapidly, and this was attributed to a further reduction in venous return. Since abdominal compression reversed these effects and rendered the dog BCG normal, we had reason to believe it did so by squeezing blood out of the splanchnic bed into the general circulation, resulting in improved venous return, cardiac filling, and output.

When these observations were made, we were not aware that the circulatory effects of abdominal compression during anesthesia had been investigated, but the subject was rather carefully studied by Hill[88] and Hill and Barnard[98] before the turn of the century.

As far as can be determined, theirs was the first systematic study of the effects of gravity on the circulation. This work was quite remarkable considering the fact that it was done before the carotid sinus mechanism was discovered and at a time when little was known about shock, the control of the peripheral circulation, the blood reservoir function of various organs and beds. They were concerned primarily with vasomotor compensation for gravity and studied this in various animal species (rabbits, cats, dogs, and monkeys) by measuring changes in venous and arterial pressure in different parts of the systemic circulation as a result of tilting the animal to head-up or head-down positions. Effects on vasomotor compensation were determined during anesthesia (ether and/or chloroform), after section of the spinal cord (T_3), after cutting the splanchnic nerve, and during other procedures which altered vasomotor compensation. The results obtained seem to justify, among others, the following conclusions: (1) that the force of gravity must be regarded as a cardinal factor in dealing with the circulation of the blood, (2) that the important duty of compensating for the simple hydrostatic effects of gravity in changes of position must be ascribed to the splanchnic vasomotor mechanism, (3) that the amount of compensation depends largely on individual differences, being far more complete in upright animals such as the monkey (and probably man) than in rabbits, cats, and dogs, (4) that the influence of gravity becomes of vital importance when the power of vasoconstriction is damaged by paralysis of the splanchnic vasoconstrictors, induced by severe operative procedures or by cutting the spinal cord, by asphyxia, or by poisons such as chloroform, ether, and curare, (5) that, when vasomotor compensation is destroyed and the animal is placed in the foot-down position, the blood drains into the abdominal veins, the heart empties, and the cerebral circulation ceases, but these effects can be reversed either by placing the animal in a head-down position *or by firmly bandaging the abdomen*, and (6) that while chloroform damages the heart and ether does not, both of these produce a paralysis of the compensatory vasomotor mechanism which lasts for a considerable time after these anesthetics are stopped. These investigators clearly demonstrated the importance of the splanchnic bed in the reflex control of the circulation. They found that after spinal cord section, if dogs were placed in the foot-down position,

blood pressure dropped to zero and virtually the whole blood volume accumulated in the capacious abdominal venous reservoirs, but that this could be prevented by pressure on the abdomen. The effects of gravity were greater after cord section than after cutting the splanchnic nerves, and they thought this was due to abolition of tone of the abdominal muscles and to diminished effectiveness of the "respiratory pump" when the spinal cord was cut. This explanation was supported by experiments on animals after the splanchnic nerves were cut. In the foot-down position arterial pressure fell to a rather low level, returned to normal during abdominal compression, but again fell to its previous level when the compression was released. When the support of the abdomen was reduced by making a long midline abdominal incision, there was a further fall in blood pressure, and on opening the pleural cavity it fell to zero. Similar, though less marked, effects were observed in intact dogs in the head-up position after opening the abdomen.

Hill and Barnard emphasized as early as 1897, the importance of the "respiratory pump" in venous return, a view which now seems generally accepted.[75]

Although Hill and Barnard demonstrated that both ether and chloroform can destroy compensatory vasomotor control, they did not study animals under barbiturate anesthesia. However, their results have since been confirmed by others, including Gordh,[13] who found that the circulatory effects of intravenous barbiturate anesthesia were somewhat greater than those of ether. This difference in magnitude may depend on the behavior of the spleen, for in animals under barbiturate anesthesia there is dilatation of the spleen, whereas during ether anesthesia the spleen contracts and thereby diverts some blood into the general circulation.[74,113] Gordh also observed pooling of blood in the liver and abdominal veins during deep anesthesia in the rabbit. In the head-up position further pooling in these areas occurred, but this and the other circulatory effects could be reversed by abdominal compression or by tilting to the head-down position.

Information is limited as to the relative quantities of blood pooled in the splanchnic and peripheral vascular beds when neurogenic control of the circulation is partially abolished by anesthetics, blocking agents, or surgery. Hill's belief that in animals peripheral pooling is insignificant compared with that in the splanchnic reservoir was not actually based on volume measurements of abdominal contents or extremities. Although this opinion receives some support from results obtained by others,[13,85,86] increased limb volume has also been observed in animals during anesthesia.[115] In man it seems likely that some blood is pooled in the lower extremities as well as in the abdomen, and this is almost certainly true in the erect posture.[13]

Counter pressure (water boot) applied to the lower extremity alone has been found to prevent postural hypotension in patients following sympathectomy.[110] On the other hand, there does not seem to be any greater pooling of blood in the legs of patients with idiopathic postural hypotension than in normal individuals while standing.[42] Supporting both legs and abdomen is known to be effective in postural hypotension of the idiopathic type[42,43] as well as in that following sympathectomy or ganglionic blocking agents, but there is limited information about the effect of abdominal compression alone during general and spinal anesthesia.

In any case, the evidence presented indicates that abdominal compression improves circulatory function when the circulation is depressed through loss of vasomotor tone and control. Improvement in venous return, cardiac output, and arterial pressure is most likely due to a reduction in capacity of the abdominal vascular bed and an increased venous pressure gradient produced by applying pressure extrinsically. Thus, the initial effect would be a kind of autotransfusion from the overly distended splanchnic bed, while the maintenance of pressure would prevent the reaccumulation of blood in this area. It seems unlikely that compressing the abdomen could have any significant direct effect on splanchnic arteriolar resistance. Abdominal compression appears to facilitate venous return by increasing the venous pressure gradient, even when the mean intrathoracic pressure is increased by intermittent positive pressure artificial respiration.[87]

It could be argued that these observations on the effects of light abdominal pressure support the view[87,102] that good abdominal muscle tone is important in venous return and circulatory function. However appealing this concept may be, proof for it has been difficult to obtain.

If abdominal compression does enhance venous return, as we believe, when the integrity of the vasomotor control system is compromised, then this procedure and its implications should be of practical as well as academic interest. Most investigative work on animals must be carried out during anesthesia, which is known to depress the circulation and alter its compensatory responses, and this may therefore affect the results obtained. In human beings the importance of the patient's position on the operating table has been emphasized by Gordh[13] and others. It may prove wise during surgery on human patients or on animals, where conditions permit, to tilt the head down slightly and/or to apply abdominal compression, especially when deep anesthesia is necessary or when venous return is impaired by loss of blood or artificial respiration. These procedures should not be used, however, in the presence of congestive heart failure.

Finally, if the observations described are being interpreted correctly, ballistocardiographic methods should prove quite useful in evaluating anesthetic agents and other drugs both in man and in the experimental animal.

SUMMARY

1. Studies were carried out on dogs under morphine-barbiturate anesthesia to determine the nature and variability of the dog ballistocardiogram and to relate these records temporally to various cardiovascular events. The ballistocardiograms were of the acceleration type obtained with an ultra-low frequency suspension designed for dogs.

2. The wave form of ballistocardiograms from anesthetized dogs was found to be highly variable. Among the variables tested were type of respiration (normal and artificial), position of dog on bed, tightness of coupling between dog and bed, and duration of the experiment. In most cases, ballistocardiograms were either "abnormal" at the outset of an experiment, or became so later; the degree of abnormality seemed related to the duration of the experiment. Positive pressure artificial respiration hastened the onset and increased the degree of abnormality.

3. The use of abdominal compression (binder with or without an inflatable cuff) almost invariably prevented the usual deterioration of the ballistocardiogram, or if already abnormal, reverted it to normal. Similar results were observed during both normal breathing and artificial respiration.

4. Pressures (air and venous) were recorded in a few instances from the abdomen and thorax. Abdominal compression increased pressures in both areas, but the rise in abdominal pressure was somewhat greater, resulting in an increase in the pressure gradient between abdomen and thorax.

5. The circulatory effects of morphine-barbiturate anesthesia, artificial respiration, and abdominal compression are reviewed.

6. It is suggested that the progressive deterioration of the ballistocardiogram of the anesthetized dog is a reflection of anesthesia-induced circulatory depression resulting in pooling of blood in extrathoracic areas, and reduction in venous return, cardiac output, and arterial pressure. The improvement of the ballistocardiogram from dogs under anesthesia when abdominal compression is applied suggests that this procedure improves circulatory function by diverting blood pooled in the splanchnic bed into the general circulation, thereby enhancing venous return and cardiac output.

The author wishes to express his gratitude to a number of medical students who provided very valuable assistance in collecting the data set forth in this report. They include John Thomas, Roger Freeman, John Bateman, Elliott Robbins, and Arthur Kamii. Salle A. Scarborough and Mary Emory Eysmans provided technical and secretarial assistance.

REFERENCES

1. Hamilton, W. F., et al.: Am. J. Physiol. **144**:557, 1945.
2. Cossio, P., Berreta, J. A., and Mosso, H. E.: Am. Heart J. **49**:72, 1955.
3. Frederick, W. H., Thomas, H. D., Knowles, J. L., Tucker, W. T., and Eddleman, E. E., Jr.: Am. Heart J. **50**:416, 1955.
4. Thomas, H. D., Frederick, W. H., Knowles, J. L., Reeves, T. J., Pappas, R., and Eddleman, E. E., Jr.: Am. Heart J. **50**:424, 1955.
5. Thomas, H. D., Frederick, W. H., Pappas, A. R., Real, J. D., and Eddleman, E. E., Jr.: Am. Heart J. **51**:562, 1956.
6. Darby, T. D., Goldberg, L. I., Gazes, P. C., and Arbeit, S. R.: Proc. Soc. Exper. Biol. & Med. **86**:673, 1954.
7. Honig, C. R., and Tenney, S. M.: Am. Heart J. **52**:167, 1956.
8. Scarborough, Wm. R., and Talbot, S. A.: Circulation **14**:435, 1956.
9. Hanlon, C. R., Johns, T. N. P., and Thomas, V.: J. Thoracic Surg. **19**:887, 1950.
10. Boyd, T. C., and Patras, M.: Am. J. Physiol. **134**:74, 1941.
11. Shuler, R., et al.: Am. J. Physiol. **137**:602, 1942.
12. Lauson, H. D., et al.: Am. J. Med. **1**:315, 1946.
13. Gordh, T.: Acta chir. scandinav. (supp. 102) **92**:1, 1945.
14. Gruber, C. M.: J. Pharmacol. & Exper. Therap. **60**:143, 1937.
15. Prime, F. J., and Gray, T. C.: Brit. J. Anesth. **24**:101, 1952.
16. Reynolds, C., and Veal, J. R.: Proc. Soc. Exper. Biol. & Med. **37**:627, 1938.
17. Emmelin, N.: Acta physiol. scandinav. **2**:299, 1941.
18. Kohn, R., and Lederer, L.: J. Lab. & Clin. Med. **23**:717, 1938.
19. Fieldman, E. J., Ridley, R. W., and Wood, E. H.: Anesthesiology **16**:473, 1955.
20. Etstein, B., and Li, T. H.: J. Clin. Invest. **34**:500, 1955.
21. Price, H. L., et al.: J. Appl. Physiol. **4**:629, 1952.
22. Gordh, T.: Personal communication to Johnson.[24]
23. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2, New York, 1955, The Macmillan Company.
24. Johnson, S. R.: Acta. chir. scandinav. 1951, supp. 158.
25. Shore, R., Holt, J. P., and Knoefel, P. K.: Am. J. Physiol. **43**:709, 1945.
26. Woodbury, R. A., and Nash, C. B.: (Abstract) Circulation **12**:791. 1955.
27. Winchell, P., et al.: Circulation **4**:229, 1951.

28. Hickam, J. B., and Pryor, W. W.: J. Clin. Invest. **30**:401, 1951.
29. Glazer, E. M., et al.: Clin. Sc. **13**:461, 1954.
30. Sjostrand, T.: Physiol. Rev. **33**:202, 1953.
31. Scarborough, Wm. R., and co-workers: Unpublished observations.
32. Cournand, A., et al.: Am. J. Physiol. **152**:162, 1948.
33. Otis, A. B., et al.: J. Clin. Invest **25**:413, 1946.
34. Brecher, G. A.: Venous Return, New York, 1956, Grune and Stratton, Inc.
35. Maloney, J. V., Jr., and Handford, S. W.: J. Appl. Physiol. **6**:453, 1954.
36. Holt, J. P., et al.: Am. J. Physiol. **146**:410, 1946.
37. Drew, J. H., Dripps, R. D., and Comrae, J. H., Jr.: Anesthesiology **7**:44, 1946.
38. Hill, L.: J. Physiol. **18**:15, 1895.
39. Herrick, J. F., Essex, H. E., and Baldes, E. J.: Am. J. Physiol. **101**:213, 1932.
40. Smith, H. W., et al.: J. Clin. Invest. **18**:326, 1939.
41. Pugh, L. G. C., and Wyndham, C. L.: Clin. Sc. **9**:189, 1950.
42. Stead, E. A., Jr., and Ebert, R. V.: Arch. Int. Med. **67**:546, 1941.
43. Ellis, L. B., and Haynes, F. W.: Arch. Int. Med. **58**:773, 1936.
44. Fowler, N. O., et al.: J. Clin. Invest. **29**:1387, 1950.
45. Werko, L., et al.: Lancet **2**:470, 1951.
46. Grob, D., et al.: Circulation **8**:352, 1953.
47. Crumpton, C. W., et al.: Circulation Res. **2**:79, 1954.
48. Crosley, A. P., Jr., et al.: (Abstract) Circulation **12**:690, 1955.
49. Smith, J. R., and Hoobler, S. W.: Circulation **14**:1061, 1956.
50. Bradley, S. E.: Integration of the Splanchnic Circulation in Systemic Hemodynamic Adjustments. Proceedings of the Annual Meeting, Council for High Blood Pressure Research, American Heart Association, June, 1956.
51. Freis, E. D., et al.: J. Clin. Invest. **32**:1285, 1953.
52. Mottu, T.: Am. Heart J. **47**:270, 1954.
53. Cominsky, B., et al.: J. Clin. Invest. (Abstract) **33**:924, 1954.
54. Ebert, R. V., et al., Circulation Res. **3**:378, 1955.
55. Green, H. D., et al.: Am. J. Physiol. **140**:177, 1943.
56. Pender, J. W., and Lundy, J. S.: Anesthesiology **5**:163, 1944.
57. Gregerson, M. I.: Am. J. Med. **15**:785, 1953.
58. Reeve, E. B., Gregerson, M. I., Allen, T. H., and Sear, H.: Am. J. Physiol. **175**:195, 1953.
59. Landis, E. M., and Hortenstine, J. C.: Physiol. Rev. **30**:1, 1950.
60. Bard, P., editor: Medical Physiology, ed. 10, St. Louis, 1956, C. V. Mosby Company.
61. Daniel, P. M., and Prichard, M. M. L.: J. Physiol. **114**:538, 1951.
62. Franklin, K. J., and McLachlin, A. D.: J. Physiol. **86**:381, 1936.
63. Peterson, L. H.: Fed. Proc. **11**:22, 1952.
64. Alexander, R. S.: Circulation Res. **2**:405, 1954.
65. Alexander, R. S.: Circulation Res. **3**:181, 1955.
66. Folkow, B.: Physiol. Rev. **35**:629, 1955.
67. Duggan, J. J., Love, V. L., and Lyons, R. H.: Circulation **7**:869, 1953.
68. Burch, G. E., and Murtadha, M.: Am. Heart J. **51**:807, 1956.
69. Page, E. B., et al.: Circulation **11**:262, 1955.
70. Page, E. B., Hickam, J. B., and Pryor, W. W.: The Role of the Venomotor Activity in Circulatory Adjustments. Proceedings, American Society Clinical Investigation, (Abstract) May, 1954, p. 47.
71. Bolton, B., Carmichael, E. A., and Sturup, G.: J. Physiol. **86**:83, 1936.
72. Barcroft, H., and Swan, H. J. C.: Sympathetic Control of Human Blood Vessels. Monographs of the Physiological Society, London, 1953, Edward Arnold.
73. Rashkind, W. J., et al.: Am. J. Physiol. **175**:415, 1953.
74. Silfverskiöld, B. P.: Skandinav. Arch. f. Physiol. (supp. 14, p. 1) **79**: 1938.
75. Wiggers, C. J.: Physiology in Health and Disease, ed. 5, Philadelphia, 1949, Lea & Febiger.
76. Guyton, A. C.: World Trends in Cardiology, III, Blood Volume and Contractile Protein in Heart Muscle, New York, 1956, Hoeber-Harper, p. 32.
77. Freis, E. D., and Rose, J. C.: Am. J. Med. **22**:175, 1957.
78. Thomas, W. D., and Essex, H. F.: Am. J. Physiol. **158**:303, 1949.
79. Goltz, F.: Virchows Arch. path. Anat. **29**:394, 1864.
80. Fleisch, A.: Pflüger's arch. f.d. ges. Physiol. **226**:393, 1931.
81. Heymans, C., Bouckaert, J. J., and Regniers, P.: Le sinus carotidien, et la zone homologue cardio-aortique. Paris, 1933, Doin et Cie.
82. Kelly, R. T., Freis, E. D., and Higgins, T. F.: Circulation **7**:169, 1953.
83. Burch, R. R.: Circulation **11**:271, 1955.
84. Burch, G. E.: Arch. Int. Med. **94**:724, 1954.
85. Edholm, O. G.: J. Physiol. **101**:1, 1942.
86. Edholm, O. G., and McDowall, R. J. S.: J. Physiol. **86**:80, 1936.
87. Bjurstedt, H.: Acta. physiol. scandinav. **29**:145, 1953.

88. Williams, A. H., and Gropper, A. L.: Circulation **4**:278, 1951.
89. Sarnoff, S. J., Berglund, E., and Sarnoff, L. C.: J. Appl. Physiol. **5**:367, 1953.
90. Hamilton, W. F., Woodbury, R. A., and Vogt, E.: Am. J. Physiol. **125**:130, 1939.
91. McLean, L. D., Brackney, E. L., and Visscher, M. B.: J. Appl. Physiol. **9**:237, 1956.
92. Wade, O. L., et al.: Clin. Sc. **15**:457, 1956.
93. Fowler, R. C., Guillet, M., and Rahn, H.: AF Tech. Rep. **6528**:522, 1951.
94. Bahnson, H. T.: AF Tech. Rep. **6528**:518, 1951.
95. Fenn, W., et al.: Am. J. Physiol. **151**:258, 1947.
96. Starr, I., and Friedland, C. K.: J. Clin. Invest. **25**:53, 1946.
97. Krogh, A.: Skandinav. Arch. f. Physiol. **27**:227, 1912.
98. Hill, L., and Barnard, H.: J. Physiol. **21**:323, 1897.
99. Alexander, R. S.: Am. J. Physiol. **167**:738, 1951.
100. Kerr, W. J.: Radiology **39**:153, 1942.
101. Kerr, W. J.: Texas J. Med. **37**:711, 1942.
102. Kerr, W. J., Cannon, E. F., and Lagen, J. B.: Tr. A. Am. Physicians **54**:225, 1939.
103. Kerr, W. J., and Lagen, J. B.: Ann. Int. Med. **10**:569, 1936.
104. Kerr, W. J., and Lagen, J. B.: J. Lab. & Clin. Med. **22**:1121, 1937.
105. Kerr, W. J.: Am. Heart J. **16**:544, 1938.
106. Starr, I.: Discussion of paper by Kerr, W. J., et al.: Tr. A. Am. Physicians **54**:225, 1939.
107. Dock, W., Mandelbaum, H., and Mandelbaum, R. A.: J.A.M.A. **146**:1284, 1952.
108. Scarborough, Wm. R., Mason, R. E., Davis, F. W., Jr., Singewald, M. L., Baker, B. M., Jr., and Lore, S. A.: Am. Heart J. **44**:645, 1952.
109. Taymor, R. C., et al.: J.A.M.A. **148**: 419, 1952.
110. Brown, H. R., Jr., de Lalla, V., Jr., Epstein, M. A., and Hoffman, M. J.: Clinical Ballistocardiography, New York, 1952, The Macmillan Company.
111. McCann, W. S.: Am. J. Med. **8**:62, 1950.
112. Scarborough, W. R., et al.: Am. Heart J. **45**:161, 1953.
113. Hausner, E., Essex, H. E., and Mann, F. C.: Am. J. Physiol. **121**:387, 1938.
114. Bradley, S. E., Marks, P. A., Peynell, P. C., and Meltzer, J.: Tr. A. Am. Physicians **66**:294, 1953.
115. Gruber, C. M., and Baskett, R. F.: J. Lab. & Clin. Med. **10**:630, 1924.

INFLUENCE OF THE LIMBS ON THE BALLISTOCARDIOGRAM

C. R. Honig, M.D., and S. M. Tenney, M.D.

Rochester, N. Y.

INTRODUCTION

THE physical analysis upon which modern ballistocardiography is based assumes the body to be a single mass elastically coupled to its support.[1-3] Although this assumption holds at low frequencies, forces above 15 c.p.s. move body parts with respect to one another.[4,5] Despite this departure from theory, higher frequencies must be recorded for meaningful ballistocardiography. Central flow pulses contain components up to at least 25 c.p.s.,[6] and higher frequencies are often necessary to distinguish sequential physiologic events.[7] In this report ballistocardiograms of limbless adults are used to: (1) evaluate distortion produced by disintegration of the theoretical "total body mass," (2) elucidate the physical significance of pre-ejection waves, and (3) determine the physiologic role of the limbs in the genesis of the ballistocardiogram.

METHODS

All records were made and calibrated with an ultralow-frequency instrument as previously described.[7,8] The sum of mean longitudinal and lateral I-J deflections was taken as the magnitude of frontal plane force. Patients 1 to 4 were fixed to the platform with firmly applied longitudinal and lateral shoulder plates. Although ballistocardiograms of normal subjects so restrained are not appreciably altered by application of a foot plate, absence of foot fixation might conceivably impair body-platform coupling if body weight is small. Since this would tend to decrease ballistic amplitude and attenuate high frequency components, only the reverse changes in amplitude and wave form were considered significant in comparing limbless and normal subjects.

Patients 1 and 2 were physically active, fully rehabilitated young adults with complete traumatic amputation of both thighs. Patient 3 had congenitally absent lower extremities and a 10 cm. left arm bud. Muscles of the normally formed right arm were well developed. Patient 4, a circus performer, had complete ectromelia. All were free of complicating medical illnesses or associated congenital defects. Patient 4 could be examined only once, but the others were observed on 3 separate days, and were thoroughly familiar with the laboratory and its personnel. Twenty normal subjects in the same age group served as controls.

RESULTS

A. *Quantitative Observations.*—In constructing normal standards for force one must consider differences in body shape as well as size.[8] Since surface area is difficult to measure in these subjects, an approximation has been computed by

---

From the Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

This work was supported by the United States Air Force under Contract No. AF 33 (616) 2485, monitored by the Aero Medical Laboratory, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio, and a research grant from the National Heart Institute, U. S. Public Health Service.

Received for publication April 3, 1957.

squaring the cube root of body weight, an accepted procedure in quantitative metabolism.[9] The quotient—force/weight$^{2/3}$—was termed "force index" and in 20 normal subjects it compared favorably with force/surface area (Table I). For the purposes of this report normal limits are defined by the arithmetic mean ± 2 standard deviations.

TABLE I. ANTHROPOMETRIC DATA AND FRONTAL PLANE FORCE IN 20 NORMAL SUBJECTS

PATIENT NUMBER	AGE (YEARS)	SEX	SURFACE AREA M.^{2}	WEIGHT$^{2/3}$ (KG.)	LONGITUDINAL (DYNES x 10^5)	LATERAL (DYNES x 10^5)	Σ LONGITUDINAL LATERAL	Σ LONGITUDINAL LATERAL / S.A.	FORCE INDEX
1.	38	M	2.20	21.3	11.2	8.3	19.5	8.9	9.2
2.	24	M	1.94	18.2	11.9	8.9	20.8	10.7	11.4
3.	19	M	1.84	16.3	10.5	9.3	19.8	10.7	12.2
4.	32	M	1.77	16.7	11.8	8.4	20.2	10.4	12.1
5.	40	M	2.00	18.5	10.2	9.0	19.2	9.6	10.4
6.	42	M	1.84	18.2	12.3	6.2	18.4	10.0	10.1
7.	24	F	1.54	14.0	7.7	4.0	11.7	7.6	8.4
8.	28	M	2.30	20.2	14.1	11.1	25.2	10.9	12.3
9.	41	F	1.59	15.5	9.2	5.7	14.9	9.4	9.6
10.	40	F	1.90	17.4	11.8	8.1	19.9	10.5	11.4
11.	41	F	2.05	21.5	11.5	8.5	20.0	9.8	9.3
12.	30	F	1.52	14.2	7.3	5.2	12.5	8.2	8.8
13.	29	M	2.00	18.8	9.6	7.4	17.0	8.5	9.1
14.	25	F	1.68	15.3	8.9	7.4	16.3	9.7	9.3
15.	30	M	1.86	17.5	10.6	8.8	19.4	10.3	11.1
16.	33	F	1.75	15.8	9.9	5.8	15.7	9.0	10.0
17.	32	M	1.84	16.8	11.0	8.6	19.7	10.7	11.7
18.	25	M	1.84	17.2	11.4	7.2	18.6	10.2	10.8
19.	28	M	1.65	16.5	12.8	6.4	19.2	11.6	11.6
20.	28	M	1.85	17.8	10.2	9.8	20.0	10.8	11.2
Mean							18.3	9.9	10.5
1 Standard Deviation							±2.9	±1.0	±1.2

As demonstrated in Table II the force index was abnormally high in each limbless subject. This was neither a statistical artifact of size correction nor a weight dependent artifact in the apparatus because: (1) In Patient 1 frontal plane force uncorrected for body size exceeded maximum normal. (2) In Patients 1 and 2 force was abnormally high even when divided by that surface area which existed prior to amputation. (3) In Patient 3 surface area calculated from oxygen consumption yielded values of force/surface area even larger with respect to normal than force/weight$^{2/3}$. (4) The force index of children of comparable body weight fell within the adult normal range.

An increase of platform inertia should decrease ballistic amplitude, attenuate high frequencies, and distort wave form.[1-3] Since the limbs add inertia to the system, their absence might account for the observed increase in force. In order to simulate limb loading, up to 20 Kg. of dead weight were added to the platform in stepwise fashion. Though force decreased as expected, wave form deteriorated before normal amplitude was attained.

Two subjects demonstrated increased respiratory variation, and in 2 an abnormal preponderance of lateral force was apparent, features which are definitely abnormal in patients under 40 years of age.[8]

B. *Qualitative Observations.*—Representative oscillographic records for each patient are displayed in Fig. 1; vertical lines denote the time of electrocardiographic R wave, upright and inverted arrows indicate inspiration and expiration, respectively.

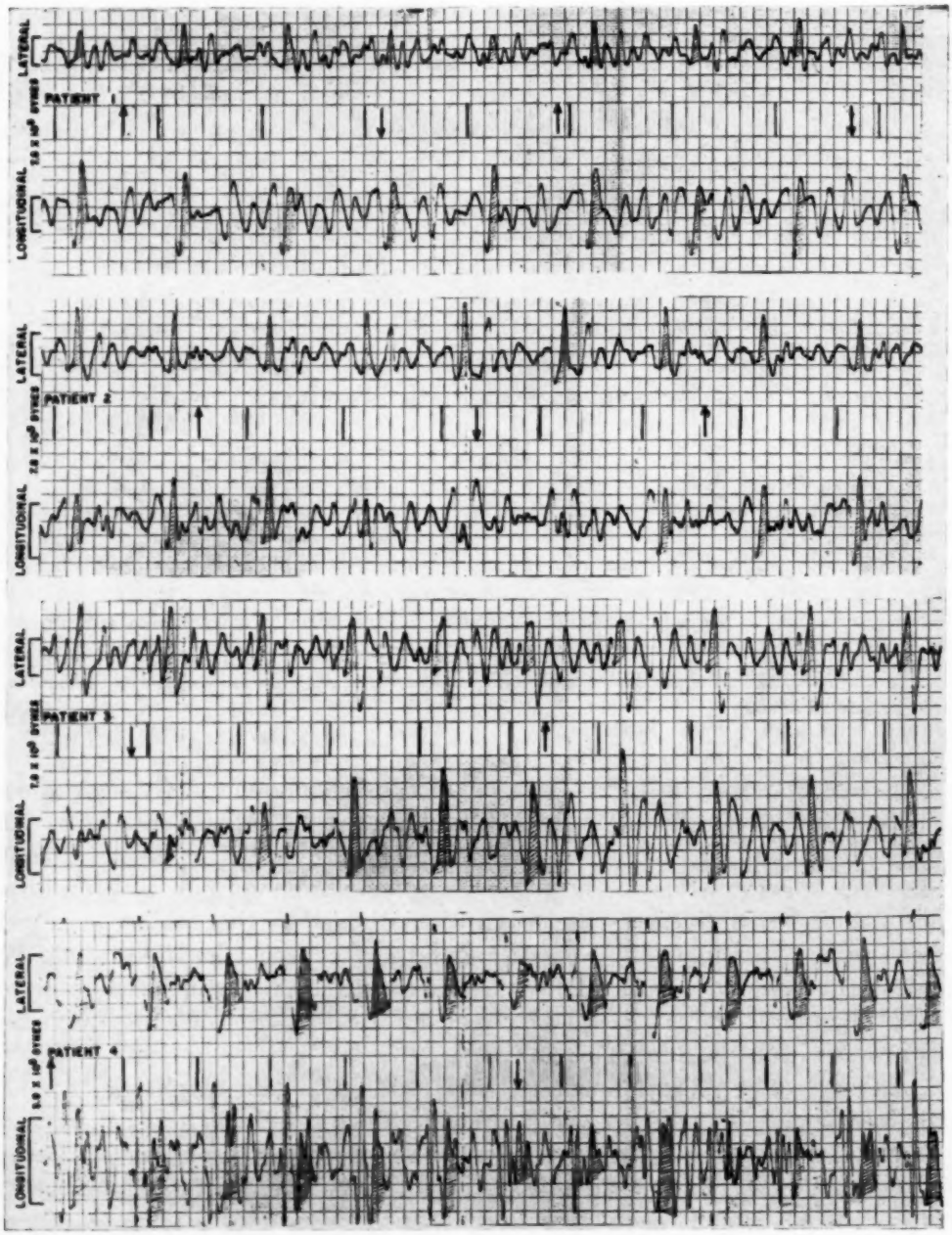


Fig. 1.—Ultralow-frequency ballistocardiograms in 4 ectromelic patients.

All limbless subjects exhibited abnormal ballistic respiratory variation as to morphology, particularly in longitudinal records. Pre-ejection waves were normal except for Patient 4 in whom amplitude and complexity were markedly increased despite normal first sound and apex impulse. The most striking abnormality was the presence of large diastolic vibrations which "rode in" to cancel or reinforce end-systolic deflections. Their frequency was in direct proportion to trunk length: 8 c.p.s. in Patients 1 and 2; 9 c.p.s. in Patient 3; and 11 c.p.s. in Patient 4.

TABLE II. ANTHROPOMETRIC DATA AND FRONTAL PLANE FORCE IN ECTROMELIA

PATIENT NUMBER	AGE (YEARS)	SEX	SURFACE AREA WITH LEGS—M.^{2}	NUMBER OF LIMBS	HEIGHT (CM.)	WEIGHT (KG.)	WEIGHT$^{2/3}$ (KG.)	LONGITUDINAL (DYNES x 10^5)	LATERAL (DYNES x 10^6)	Σ LATERAL LONGITUDINAL	FORCE INDEX
1.	36	M	2.08	2	94	76	17.9	18.7	16.7	35.4	19.8
2.	41	M	1.76	2	92	57	14.8	10.0	12.6	22.6	15.3
3.	37	M	—	1	80	54	14.1	11.4	10.6	21.9	15.4
4.	32	F	—	0	59	16	6.2	8.1	15.1	23.2	37.7
Mean								12.1	13.7	25.8	22.1

DISCUSSION

Talbot and Harrison,[4] in their critique of current methods, conclude that relative motion of body parts distorts all ballistocardiograms through summation, complex mass, and loading effects. Our data strongly support this view. Four subjects with ectromelia exhibited marked increases in I-J amplitude relative to normal subjects, despite reduced cardiac size and output. Such an increase in measured reaction force, despite probable decrease in force generated at the heart, might be due to (1) change in force direction or balance, (2) change in the internal or external mechanical properties of the body. The data cannot be explained by a shift of anteroposterior forces into the frontal plane, for the measured increase considerably exceeds the sum of maximum normal frontal and sagittal plane forces. If increased ballistic amplitude in the limbless were due to a change in force balance, the increase should have been greater in Patients 1 and 2 who were asymetrically deformed than in Patient 4 with complete ectromelia. Instead, Patient 4 exhibited a force index more than twice that of any other subject. The obvious difference between patients and normal persons is the absence of limbs in the body's external mechanical network. It is therefore of interest that ballistocardiograms of children of comparable body weight are qualitatively and quantitatively indistinguishable from those of normal adults.[8] Weighting the platform to simulate limb loading does not reproduce the whole body ballistocardiogram, indicating the importance of the elastic coupling between limbs and trunk.

It is possible that the enhanced body motion of the limbless subject reflects change in the internal, as well as external mechanical constants of the body. If the coupling between cardiovascular system and body shell were less compliant, the efficiency of kinetic energy transfer would be increased and both the fidelity

and amplitude of the ballistocardiogram would be enhanced. Through the courtesy of Dr. Henry H. Kessler the autopsy protocol of a congenital complete ectromelic was made available to us.[10] This patient's descending aorta was hypoplastic, particularly beyond the renal arteries; the internal iliacs were barely patent. If aortic capacity were decreased more than volume flow, a state of chronic overdistention would result. It is therefore of interest that Dr. Kessler's patient exhibited dilatation of the proximal aorta. Increase in aortic cross section would tend to increase the elastic coefficient of the adventitial envelope binding aorta to body shell, and decrease transmissional loss of kinetic energy. In support of this formulation, distention of the aorta through acute arteriolar constriction improved the correlation between metered blood flow and the canine ballistocardiogram.[11]

The large complex pre-ejection waves of Patient 4 suggest that high-frequency vibrations may be attenuated in whole body recordings. It is unlikely that A-V valve closure or isometric contraction could generate forces greater than those of normal subjects, for the patient's heart is small and her apex beat unremarkable. Early systolic waves are originated by brief, rapidly changing events, and therefore consist principally of high-frequency vibrations. In normal individuals and in heavy incomplete ectromelics, inertia as well as complex mass and loading effects markedly attenuate frequencies above 15 c.p.s.[4] In contrast, the high-frequency vibrations comprising pre-ejection events were well recorded in Patient 4 who weighs but 16 kilograms and whose internal and external mechanical networks are altered as described above. Pre-ejection waves in this patient actually exceeded I-J in magnitude, and might have been even larger had the the ratio of platform to subject weight been smaller.[2] This does not necessarily mean that *forces* generated by cardiac motion and valve closure exceeded those originated by ejection, for in an elastic system the effects of brief impact vary with the time course of force application. The biologic effects of various rates of force application have been thoroughly studied in conjunction with parachute, ejection seat, and catapult design,[12] and have been discussed with respect to the ballistic diastolic complex.[11] Therefore, the authors believe that the pre-ejection vibrations originated by valve closure are not directly comparable with the I-J deflection, for the former has the dimensions of mass times jolt, the latter the dimensions of mass times acceleration.

Increased amplitude and improved wave form definition in limbless subjects indicates that the ballistocardiogram is originated by events anatomically close to the heart, and that the elastically coupled limb masses distort whole body recordings. We therefore believe that ballistocardiography would be advanced by relinquishing whole body instrumentation and interpretation, an idea previously expressed by Talbot and Harrison.[4]

Peterson's challenge of the classical standing wave hypothesis has reopened the problem of the mechanism of deformation of the central pressure pulse.[13] Each legless adult exhibited large diastolic waves, the frequency of which varied inversely with compression chamber length. Although these and other ballistic observations are compatible with the existence of an arterial standing wave,[11] they have no bearing on the possible additional contribution of harmonic dispersion to the genesis of the peripheral pulse.

SUMMARY AND CONCLUSIONS

1. Records obtained from 4 ectromelic and 20 normal adults were compared to determine the influence of the limbs on the ultralow-frequency force ballistocardiogram.

2. Measured reaction force was markedly increased with respect to whole body norms, despite probable decrease in force generated by the heart. This increase was not due to difference in body-platform coupling, force direction, or force balance, but reflected freedom from the impedance of the limbs. Change in the internal mechanical constants of the body may also have played a role. Although the concept of a "theoretical total body mass" may be applicable in the frequency range of displacement or even in velocity ballistocardiography, it is invalid for force ballistocardiography.

3. In the lightest subject abnormally large pre-ejection waves were observed, despite normal first sound and apex impulse. The physical significance of these waves is discussed in terms of the time factor in force application.

4. Each subject exhibited large diastolic oscillations at a frequency inversely related to compression chamber length, a finding compatible with the existence of an arterial standing wave.

5. Since the peripheral vessels do not contribute forces and the passive limb masses significantly distort whole body recordings, we believe an ultralow-frequency instrument sensing solely thoracic motion to be desirable.

REFERENCES

1. von Wittern, W. W.: Wright Air Development Center Technical Report **52**:340, 1952.
2. von Wittern, W. W.: Am. Heart J. **46**:705, 1953.
3. Burger, H. C., Nordergraaf, A., and Verhagen, A.M.W.: Am. Heart J. **46**:71, 1953.
4. Talbot, S. A. and Harrison, W. K., Jr.: Circulation **12**:1022, 1955.
5. von Wittern, W. W.: Symposium on BCG. Second World Congress of Cardiology, Washington, D. C., September, 1954.
6. Honig, C. R.: Unpublished Observations.
7. Honig, C. R. and Tenney, S. M.: Am. Heart J. **52**:167, 1956.
8. Honig, C. R. and Tenney, S. M.: Am. Heart J. **52**:343, 1956.
9. Benedict, F. G. and Talbot, F. B.: Am. J. Dis. Child. **8**:1, 1914.
10. Hospital for Crippled Children, Newark, N. J.: Autopsy Protocol No. A-1 54.
11. Honig, C. R. and Tenney, S. M.: Am. Heart J. **53**:655, 1957.
12. Gagge, A. P., and Shaw, R. S.: *in* Glasser, O.: Medical Physics, Vol. 2, Chicago, 1950, The Year Book Publishers, Inc.
13. Peterson, L. H.: Circulation **14**:982, 1956.

FACTORS INFLUENCING THE TIME OF ONSET OF THE FIRST HEART SOUND IN NORMAL SUBJECTS

MURRAY STROBER, M.D.,* FERNANDO MARTIREZ, M.D.,* AND JOHN J. KELLY, JR., M.D.**

BROOKLYN, N. Y.

IT IS now widely recognized that the onset of the first heart sound may be delayed in patients with mitral stenosis.[1-6] The interval from the beginning of ventricular depolarization to the first rapid vibrations of the first heart sound varies from 0.02 to 0.12 second in cases of mitral stenosis. This interval, which can be called the Q-1 interval from now on, does not occur in a range this wide in patients without mitral valvular lesions or conduction defects.

A previous investigation from this laboratory[6] was concerned with the factors affecting the Q-1 interval in patients with mitral stenosis. It was determined that 3 factors affect this value. They are (1) the electrical mechanical interval of the left ventricle; that is, the time from the beginning of depolarization of the ventricle to the onset of ventricular contraction, (2) the pressure differential at end-diastole between the left atrium and the left ventricle,† and (3) the rate at which the left ventricle develops pressure. In general, the lateness of the first sound paralleled the severity of the mitral stenosis. Cases of long-standing mitral stenosis may exhibit no murmurs.[6] If the mitral valve is extensively calcified, the first sound often loses its snapping quality and the opening snap may be absent.[7] The first heart sound is usually quite delayed in such instances and may provide the first clue to the correct diagnosis.

In this same study,[6] the Q-1 interval in a group of 100 patients with heart disease, but without mitral valvular lesions or bundle branch block, varied from 0.02 to 0.06 second, with a mean of 0.04 second and a standard deviation of 0.01 second. It was suggested, therefore, that in the absence of bundle branch block, which in itself may cause a delay in the first heart sound,[8,9] a Q-1 interval of 0.07 second or greater was evidence of mitral stenosis.

This work was supported by Grant H-1250 from the Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, Bethesda, Md., and the New York Heart Association.

Received for publication April 18, 1957.

*Instructor in Medicine, State University of New York, Downstate Medical Center, Brooklyn, N. Y.

**Associate Professor of Medicine, State University of New York, Downstate Medical Center, Brooklyn, N. Y.

†In normal hearts and in left ventricular failure, these pressures are about equal and only in mitral stenosis (or very rarely in a ball-valve tumor or thrombus) does the left atrial end-diastolic pressure significantly exceed the left ventricular end-diastolic pressure.

Observations of records taken from healthy laboratory personnel suggested that body size might be an important factor determining the Q-1 interval in normal subjects. Therefore, it was decided to study the relation of height, weight, sex, and the duration of the QRS complex to the Q-1 interval.

METHOD

Fifty normal males and 50 normal females between the ages of 2 and 35 years were studied. Subjects who had a history of rheumatic fever, physical findings to suggest a cardiac abnormality, or hypertension were not included. Phonocardiograms were taken with a Cambridge Simplitrol. The paper speed was 50 mm. per second, allowing an accuracy in measurement of 0.01 second. The subjects were resting in the supine position when the records were obtained. Phonocardiograms were routinely taken at the apex, Erb's point, and the pulmonic and aortic valve areas, but measurements were made from the apex readings. Limb Lead II of the electrocardiogram was recorded simultaneously with the phonocardiogram.

RESULTS

The distribution of the Q-1 interval is shown in Fig. 1. For examination of the effect of age, height, weight, heart rate, and QRS duration, the material was broken down into 4 groups, according to sex and ages (2 to 19 and 20 to 35 years).

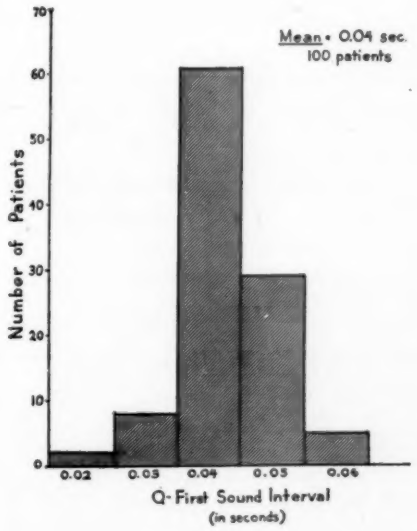


Fig. 1.—Normal patients.

The latter group was of course the more satisfactory since maximum growth, for all practical purposes, had been achieved and it was not necessary to separate the related effect of age on height, weight, heart rate, and QRS duration in this group. The group of males aged 20 to 35 years was the largest of the 4 groups, containing 40 subjects. In this group, the coefficient of correlation was calculated for the Q-1 interval versus age, height, weight, heart rate, and QRS duration.

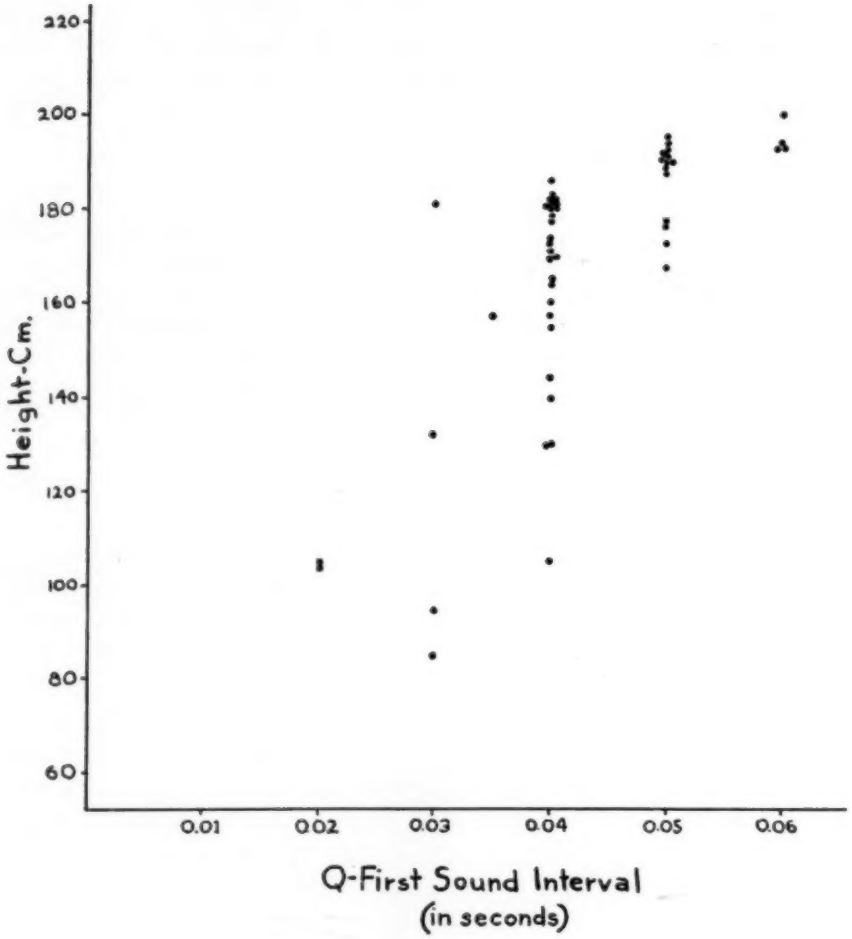


Fig. 2.—Males.

By far the best correlation was with height ($r = 0.56 \pm 0.11$). The coefficient of correlation of the Q-1 interval with the other factors analyzed were not in a significant range. For example, the coefficient of correlation with weight was 0.37, 0.20 for the QRS duration, 0.12 for age, and minus 0.22 for heart rate. Mild exercise in 5 normal adult subjects did not affect the Q-1 interval, although the heart rate of these individuals did increase. Analysis of the other subgroups was compatible with the data obtained from the group of males aged 20 to 35, although there were fewer numbers in the remaining subgroups. The heart rates of the children were considerably more rapid, creating an additional variable. There was a minimal spread of the Q-1 intervals in children since no child under the age of 10 years had a Q-1 interval greater than 0.04 second. However, if body height is plotted against the Q-1 interval for males and females, the results indicate clearly that the tallest males and females tended to have the greatest Q-1 intervals (Figs. 2 and 3).

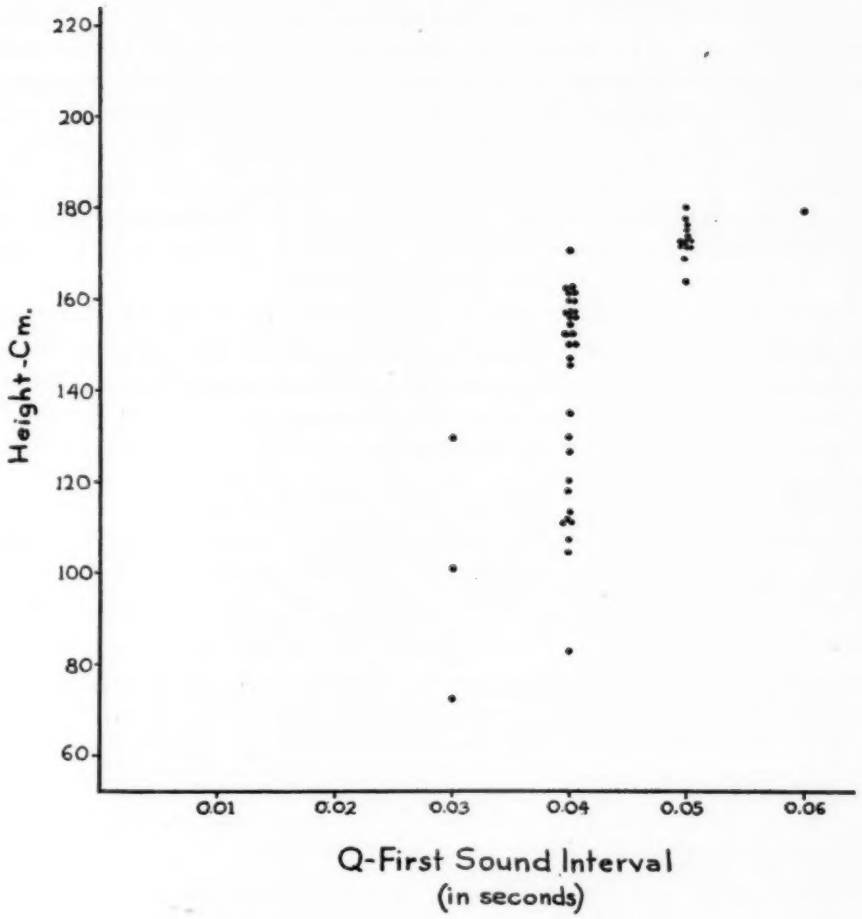


Fig. 3.—Females.

DISCUSSION

In our study of 100 normal subjects several factors seemed to influence the time of onset of the first heart sound. These factors included age, height, weight, heart rate, and QRS duration. The QRS duration increases with the growth of the child and the concomitant growth of the heart itself.[10] The Q-1 interval tended to lengthen with an increase in QRS duration, although the QRS durations were within a "normal" range (below 0.10 second). Height was the most significant factor in predicting the length of the Q-1 interval in normal subjects. Thus, in cases of suspected mitral stenosis, if reliance is to be placed on the phonocardiographic evidence of a delay in the first heart sound, it would be wise to take the patient's height into consideration. An increase in heart rate in normal subjects failed to alter the Q-1 interval, whereas an increase in heart rate in patients with mitral stenosis usually increased the Q-1 interval.

In 100 cases studied the Q-1 interval ranged from 0.02 to 0.06 second, with a mean of 0.04 second. This range is in agreement with the values of normal man compiled from various sources by Wiggers,[11] Orias and Braun-Menendez,[12] and of children by Mannheimer.[10] Some of the variations in absolute values obtained by earlier investigators were probably due to differences in the sensitivity of the recording devices.[12] The distribution graph of the Q-1 intervals (Fig. 1) is almost identical to that described by Kelly[6] for a group of 100 patients with cardiac lesions of all types except those involving the mitral valve and the conduction system.

In a review of the literature no reported correlation of the Q-1 interval with the body build could be found. In a normal population, the height of the subject is the most significant factor influencing the first heart sound interval.

SUMMARY

One hundred "normal" subjects, aged 2 to 35 years, had simultaneously recorded electrocardiograms and phonocardiograms to determine the time from the beginning of ventricular excitation to the first rapid vibrations of the first heart sound. This Q-1 interval varied directly with age, weight, and the QRS duration, but most significantly with the subject's height.

We would like to express our appreciation for the technical assistance of Mrs. Lydia Roth and Mrs. Elizabeth Murrell. We are also grateful to Dr. Brian MacMahon of the State University of New York, Downstate Medical Center, for aid in the statistical analysis of our study.

REFERENCES

1. Weiss, O., and Joachim, G.: Ztschr. klin. Med. **73**:240, 1911.
2. Luisada, A.: Am. Heart J. **22**:245, 1941.
3. Cossio, P., and Berconsky, I.: Rev. argent. de cardiol. **10**:162, 1943.
4. Messer, A. L., Counihan, T. B., Rapport, M. B., and Sprague, H. B.: Circulation **4**:576, 1951.
5. Wells, B.: Brit. Heart J. **16**:261, 1954.
6. Kelly, J. J.: Am. J. Med. **19**:862, 1955.
7. Wynn, A.: Brit. Heart J. **15**:214, 1953.
8. Lewis, T.: Quart. J. Med. **6**:441, 1912-1913.
9. Lewis, J. K.: Arch. Int. Med. **53**:741, 1934.
10. Mannheimer, E.: Acta paediat. scandinav. (Suppl. 2) **28**:16, 116, 1940.
11. Wiggers, C. J.: Philadelphia, 1923, Lea & Febiger
12. Orias, P., and Braun-Menendez, E.: The Heart Sounds in Normal and Pathologic Conditions, London, 1939, Oxford University Press.

THE RELIABILITY OF HIGH VOLTAGE OF THE QRS COMPLEX AS A DIAGNOSTIC SIGN OF LEFT VENTRICULAR HYPERTROPHY IN ADULTS

HARRY A. GRUBSCHMIDT, M.D., AND MAURICE SOKOLOW, M.D.

SAN FRANCISCO, CALIF.

HIGH voltage of the QRS complex in the left precordial leads of the electrocardiogram was clearly shown by Wilson and associates,[1] in their classic paper of 1944, to be a common finding in patients with left ventricular hypertrophy. These authors, however, presented no specific data on the differentiation of normal from abnormal voltage. A year earlier, Gubner and Ungerleider,[2] in a study using the standard limb leads only, demonstrated that in only 1 per cent of normal persons with left axis deviation did the sum of R in Lead I plus S in Lead III exceed 25 millimeters (mm.). Sokolow and Lyon,[3] in 1949, established criteria for abnormal voltage which they believed significant for the diagnosis of left ventricular hypertrophy, i.e., the sum of the R wave in V_5 or V_6 and the S wave in V_1 is greater than 35 millivolts (mv.). It is to be noted that these standards pertain only to adults, since children and adolescents normally may have high voltage of the QRS complex.

Heine and his associates,[4] in 1952, compared our electrocardiographic criteria for left ventricular hypertrophy[3] with the "roentgen-clinical diagnosis" of left ventricular hypertrophy in a group of veterans. These investigators found that the sum of R in V_5 or V_6 plus S in V_1 was greater than 35 mv. in the electrocardiograms of only 1.5 per cent of 261 patients without left ventricular hypertrophy. This abnormality was present in 71 per cent of their 149 patients with "roentgen-clinical" evidence of left ventricular hypertrophy. Scott and his associates[5] evaluated the accuracy of current electrocardiographic criteria for left ventricular hypertrophy by comparing the electrocardiographic and autopsy findings in 100 cases. These authors found that the criteria established by us permitted the recognition of left ventricular hypertrophy in 85 per cent of the 100 patients proved to have this condition at autopsy. The remaining 15 per cent had only minimal left ventricular hypertrophy. Scott pointed out that the criteria of high voltage added considerably to the number of cases recognized electrocardiographically before the typical ST-T abnormalities developed.

The present study was initiated to determine the number of "false positives," that is, to determine the reliability of these criteria when present as the sole electrocardiographic finding in patients selected at random, without previous knowledge of the clinical diagnosis.

From the Department of Medicine, University of California School of Medicine, San Francisco, Calif.

Supported in part by a research grant (H-754) from the National Heart Institute, United States Public Health Service.

Received for publication May 7, 1957.

SUBJECTS AND METHODS

Approximately 2,000 records from the files of the Electrocardiograph Department of the University of California Hospital were reviewed, and 101 patients over the age of 25 years whose electrocardiograms showed abnormal voltage as an isolated manifestation were selected for study.

No other electrocardiographic abnormality was present; in particular, records showing borderline ST-T changes or T waves less than 1 mm. in height were eliminated from the study. All records selected for study would have been interpreted as within normal limits except for the high voltage of the QRS complex. Table I lists the criteria used.

TABLE I. CRITERIA OF ABNORMAL VOLTAGE

1. The sum of the voltage of R in V_5 or V_6 plus the voltage of S in V_1 exceeds 35 mv.
2. The voltage of R in V_5 or V_6 exceeds 26 mv.
3. The voltage of R in aVL exceeds 11 mv.
4. The voltage of R in aVF exceeds 20 mv.
5. The voltage of R in Lead I plus S in Lead III exceeds 25 mv.
6. The voltage of R in Lead I exceeds 16 mv.

TABLE II. AGE RANGE IN SERIES OF 101 PATIENTS*

AGE GROUP (YEARS)	NUMBER OF PATIENTS
25-30	7
31-40	7
41-50	21
51-60	25
61-70	27
Over 70	14
	Total 101

*The sole electrocardiographic abnormality in these patients was high voltage of the QRS complex.

TABLE III. VOLTAGE ABNORMALITIES IN SERIES OF 101 PATIENTS

VOLTAGE ABNORMALITIES	NUMBER OF PATIENTS
R in V_5 or V_6 plus S in V_1 exceeded 35 mv.	73
R in V_5 or V_6 exceeded 26 mv.	55
R in aVL exceeded 11 mv.	37
R in Lead I plus S in Lead III exceeded 25 mv.	26
R in Lead I exceeded 16 mv.	15
R in aVF exceeded 20 mv.	0

The age range of the patients in the study is given in Table II. Table III lists the relative frequency of high voltages in the electrocardiograms of the patients in this series and reflects the fact that many of these records showed more than one such abnormality. It will be seen that the sum of the R wave in V_5 or V_6 and the S wave in V_1 greater than 35 mv. was the most common abnormality.

All patients had been given a physical examination by one or more of the University staff. Interpretations of the roentgen films of the chest were made by members of the Department of Radiology of the University of California Hospital. Clinical examinations, x-ray films of the chest, and electrocardiograms usually had been performed within 24 to 48 hours of each other, but in no instance were they more than 2 weeks apart. The hospital charts were reviewed for clinical and radiologic evidence of cardiac disease, or for a condition increasing the work of the left ventricle.

Table IV summarizes the clinical diagnoses in the 101 patients studied. The great majority (72 of the subjects) had cardiovascular disease secondary to hypertension; 21 of these patients had hypertensive vascular disease, as established by blood pressures exceeding 140/90 mm. Hg. Most of the patients with hypertension had blood pressures considerably in excess of this figure, the mean being 180/102 mm. Hg. Less common were rheumatic, coronary, congenital, syphilitic, or thyrotoxic heart disease. Two of the remaining 5 patients had persistent apical systolic murmurs, Grade 2 in intensity, 1 of whom had a clear-cut history of an attack of rheumatic fever in the past. Of the 3 patients who presented no recognizable cause for the electrocardiographic abnormalities, 1 had chronic nephritis of undetermined type. Thus, 95 per cent of the 101 patients had either obviously recognizable clinical cardiac disease producing a strain on the left ventricle or hypertensive vascular disease; 2 per cent had possible rheumatic heart disease with persistent apical systolic murmurs which could have represented mitral incompetence or developing aortic stenosis; and only 3 per cent had no apparent cardiac defect, although 1 patient had nephritis.

Review of the x-ray records showed that approximately 70 per cent of the routine x-ray films of the chest had been interpreted by the radiologist as evidencing left ventricular enlargement or abnormality of the contour of the left ventricle, suggesting left ventricular hypertrophy.

R/T Ratio and Ventricular Activation Time.—An R/T ratio greater than 10, which is the upper limits of normal,[6] was found in only 10 cases in the present series. The ventricular activation time in V_5 or V_6 equalled 0.05 second in 22 cases, and exceeded this figure in only 2 cases. The duration

TABLE IV. CLINICAL DIAGNOSES IN 101 PATIENTS WITH ISOLATED HIGH VOLTAGE OF THE QRS COMPLEX

Hypertensive cardiovascular disease		37
Hypertensive cardiovascular disease with angina		14
Hypertensive vascular disease		20
Hypertensive vascular disease with angina		1
Arteriosclerotic heart disease with angina		1
Rheumatic heart disease		9
Mitral	3	
Aortic	1	
Combined	5	
Congenital heart disease		2
Combinations of the above with syphilis, thyrotoxicosis, or subacute bacterial endocarditis		10
Cardiac disease, cause uncertain		2
Questionable cardiac disease (valvular ?)		2
No apparent cardiac disease		3
Total		101

of the R wave was 0.04 second or more in only 5 cases, and in only 1 of these was it 0.045 second. The small number of our cases with increased ventricular activation time or increased duration of the R wave suggests that left ventricular hypertrophy had not existed sufficiently long to produce abnormalities of these parameters, or else was so mild that it did not produce alterations in ventricular activation time or depolarization of the left ventricle.

Serial electrocardiograms in 1 patient (Fig. 1) illustrate the successive changes, beginning with high voltage of the QRS complexes, succeeded by low T waves, and finally progressing to the fully developed pattern of left ventricular hypertrophy.

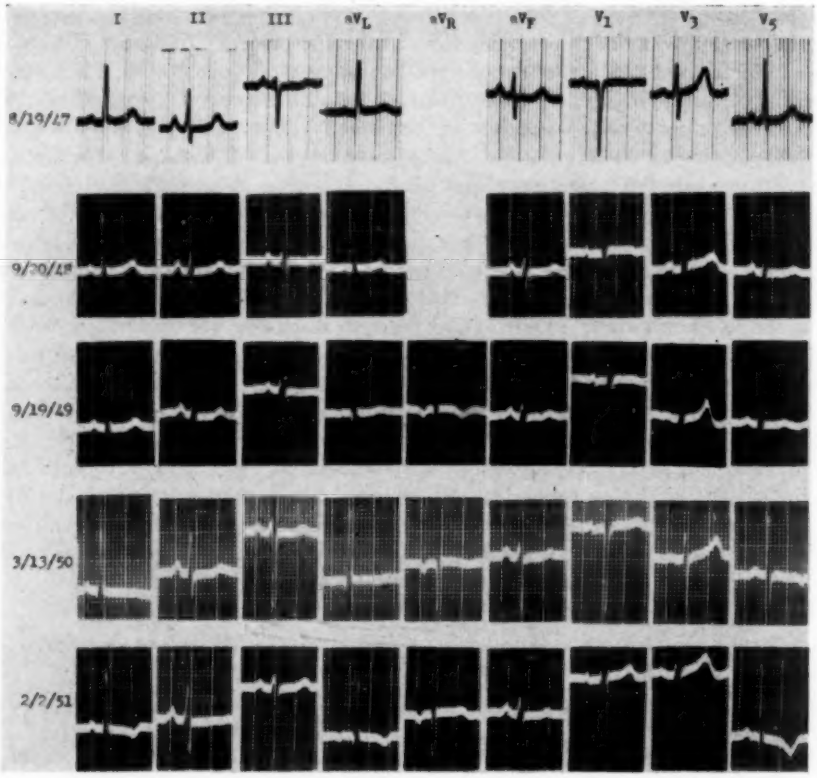


Fig. 1.—J. A., female, aged 53 years. Progressive abnormalities between 1947 and 1951. Serial chest films showed no change in the size of the heart during this period.

DISCUSSION

It is apparent from the data presented that high voltage of the QRS complexes is a reliable sign of left ventricular hypertrophy in adults. Between 95 and 98 per cent of patients selected solely on the basis of an electrocardiogram showing voltage of the QRS complexes according to the criteria listed in Table I were found to have either clinical and/or radiologic signs of disease of the heart affecting the left ventricle. This data complements published reports indicating the sensitivity of the electrocardiographic criteria for the diagnosis of left ventricular hypertrophy.[3-5]

The fact that in only 2 of the cases in this series did the ventricular activation time exceed 0.05 second, and in only 5 was the duration of R 0.04 second or more, indicates that the high voltage noted in the electrocardiogram is the earliest abnormality in developing left ventricular hypertrophy. This differs from Myers' statement that the ventricular activation time is abnormal in most cases of left ventricular hypertrophy with high voltage of the QRS complexes.[7] Sodi-Pallares found delayed ventricular activation time to be a reliable sign of left ventricular hypertrophy, but did not indicate its frequency as an isolated abnormality.[8]

The mechanism responsible for the abnormally high voltage of the QRS complexes in left ventricular hypertrophy is not completely understood. It is thought that the increased left ventricular muscle mass develops greater voltage, but in many patients with increased left ventricular mass the voltage is normal. Sodi-Pallares has attributed the increased amplitude of the QRS complexes to: (1) a greater number of activation dipoles oriented to the precordial electrode, and (2) the unopposed electrical forces of late activation of the left ventricular wall.[8]

High voltage of the QRS complex may be present in a small percentage of cases without clinical or roentgen evidence of left ventricular hypertrophy; this occurred in 2 to 5 per cent of the present series. Transient elevations of blood pressure in the past must always be excluded as a possible cause of the high voltage in hospitalized patients in whom the blood pressure has fallen to normal; in ambulatory patients past episodes of hypertension should be ruled out. We have seen patients whose blood pressure was elevated more or less consistently over a period of weeks during sustained emotional stress; once the problems were resolved, it fell to normal levels, and persisted normal for several years. During World War II we saw a number of naval personnel who had well-documented, significant hypertension as established by hospitalization on 5 or 6 occasions overseas; their blood pressure was normal during several months of close observation at a naval hospital in the United States. Conditions which increase the work of the left ventricle as a result of a high output state (such as beriberi, hyperthyroidism, severe anemia) may also increase the voltage of the QRS complexes and must be considered when high voltage is found.

It is to be re-emphasized that the criteria for high voltage employed in this paper are valid only for adults over the age of 25. In a careful analysis of the electrocardiograms of 100 normal, healthy soldiers between the ages of 20 and 25, Rapaport[9] found that the sum of the R in V_5 or V_6 and the S in V_1 was between 35 and 40 mv. in 13 per cent; in only two instances did the sum exceed 40. Thus, in persons between 20 and 25 years of age, high voltages should be considered those in excess of 40 rather than 35 mv. In none of the healthy soldiers did the voltage of R in V_5 or V_6 exceed 26 mv.

Thin-chested individuals, such as ectomorphs who have vertical hearts, are said to have a higher incidence of voltage exceeding the normal, but in our experience the criteria used in this study were valid for both vertical and horizontal hearts.

The voltage of the QRS complexes may be reduced considerably following the development of a myocardial infarction, congestive heart failure, or fluid in the pericardial or pleural cavities. The presence of one of these conditions may explain the absence of high voltage in otherwise typical examples of left ventricular hypertrophy.

SUMMARY AND CONCLUSIONS

1. A series of 101 patients who demonstrated high voltage of the QRS complex as the sole electrocardiographic abnormality, utilizing the criteria of Sokolow and Lyon,[3] were studied for presence or absence of clinical disease involving the left ventricle.

2. Ninety-five of the 101 subjects were found to have cardiovascular disease; in 72 of these patients the disease was secondary to hypertension. No apparent heart disease was present in 3 subjects; in 2 others a systolic murmur, possibly due to valvular disease, was the only abnormality found. The percentage of nonproved cardiac disease, therefore, varies from 2 to 5 per cent, depending on whether these 3 cases are included.

3. Radiologic abnormalities of the left ventricle were found in 70 per cent of the subjects in routine films of the chest.

4. High voltage of the QRS complexes was found to be an early sign of left ventricular hypertrophy, since the ventricular activation time exceeded 0.05 second in only 2 cases, and all of the cases had T waves taller than 1 mm., without ST-T abnormality.

REFERENCES

1. Wilson, F. N., et al.: Am. Heart J. **28**:621, 1944.
2. Gubner, R., and Ungerleider, H. E.: Arch. Int. Med. **72**:196, 1943.
3. Sokolow, M., and Lyon, T. P.: Am. Heart J. **37**:161, 1949.
4. Heine, W. I., Sackett, C. F., and Serber, W.: Am. J. Med. Sc. **224**:424, 1952.
5. Scott, R. C., Seiwart, V. J., Simon, D. L., and McGuire, J.: Circulation **11**:89, 1955.
6. Sokolow, M., and Friedlander, R. D.: Am. Heart J. **38**:665, 1949.
7. Myers, G. B.: The Interpretation of the Unipolar Electrocardiogram, St. Louis, 1956, C. V. Mosby Co.
8. Sodi-Pallares, D., and Calder, R. M.: New Bases of Electrocardiography, St. Louis, 1956, C. V. Mosby Co.
9. Rapaport, E.: Unpublished observations.

RECURRENCE OF TIGHT MITRAL STENOSIS SYNDROME AFTER COMMISSUROTOMY

A Report of Six Cases With Reoperation

P. Soulié, M.D.,* F. Joly, M.D.,** J. Carlotti, M.D.,** and M. Servelle, M.D.**

Paris, France

SINCE the surgical treatment of tight mitral stenosis has become a successful procedure, possibility of the recurrence of the stenosis has started various debates. In spite of the fact that some authors[6] deny the possibility of a postoperative resealing of the valve, a few well-documented cases[4,5,7,8,9] of such an occurence have been published during the past few years. In the early stages of surgery of the mitral valve most surgeons recommended beginning the procedure with a digital commissurotomy and completing it with the knife (Brock, Barley, Glover, O'Neill, Dogliotti). Later on it was recognized that a satisfactory opening could be achieved with the employment of finger fracture alone. Usually an opening of the mitral area up to two fingerbreadths was thought to give satisfactory results, and postoperative findings have supported such a concept.

In the follow-up of our patients from the clinical and hemodynamic points of view since 1950, we came to the conclusion that there was no correlation between the surgical opinion of the effectiveness of the procedure and the postoperative results.[2,10,12] On the one hand, complete surgical mitral fractures were followed by only partial hemodynamic restitution, and, on the other hand, commissurotomy judged to be incomplete anatomically gave very good clinical and hemodynamic results. It became obvious during the long-term follow-up of our operated patients that repeated postoperative catheterizations were of great value in assaying the results of mitral surgery. Especially does this fact gain great importance when the question of the possibility of mitral valve resealing is discussed. Although most of the imperfect commissurotomies manifest themselves only during a long-term follow-up, and often after initial clinical improvement, there are some few cases where the ineffectiveness of the surgical approach may be demonstrated clinically immediately.[2,12]

In this paper we intend to (1) confirm in a few cases the unquestionable re-establishment of tight mitral stenosis after a more or less prolonged period from the time of commissurotomy, and (2) discuss the exact causes and the anatomic mechanisms which contribute to the reoccurrence of stenosis, along with proof that the valves have resealed.

From the Hôpital Lariboisière, Paris, France.
Received for publication May 8, 1957.

*Professor, Faculté de Médecine de Paris, Médecin des Hôpitaux de Paris, and Director of the Center of Cardiology, Hôpital Lariboisière, Paris.
**Assistant, Center of Cardiology, Hôpital Lariboisière, Paris.

TABLE I

CASES SEX | AGE	DATES	O_2 CONSUMPTION CM.^{3}/M.	PERIPHERAL SATURATION (%)	CARDIAC OUTPUT L./M.	PRESSURES (MM. Hg) R.A.	P.A.	C.P.
1 Male 21	before C.: 7/ 7/52					50/25	(26)
	1st C.: 4/24/53						
	8 mo. later: 12/14/53	230	96	3.9	(2)	30/18 (22)	(12)
	33 mo. later: 1/ 3/56	190	93	4.6	10/4 (7)	50/25 (35)	30/23 (25)
	2nd C.: 2/10/56						
2 Female 22	before C.: 6/10/53	200	96	4.9	8/2	75/35 (50)	
	1st C.: 7/17/53						
	13 mo. later: 10/ 7/54	170	98	4.9	(3)	55/35 (40)	(32)
	27 mo. later: 12/ 3/55	150	93	2.6	12/6 (8)	90/50 (70)	50/40 (43)
	2nd C.: 12/17/55						
3 Female 23	before C.: 3/14/51	180	95	4.4	13/7	40/20 (26)	28/18 (22)
	1st C.: 4/ 9/51						
	3 mo. later: 6/22/51	180	96	4.4		36/18 (22)	(15)
	2nd C.: 12/24/54						
4 Female 32	before C.: 1/11/52	220	95	3.2		56/30 (40)	(28)
	1st C.: 2/ 1/52						
	5 mo. later: 7/16/52	210	95	4.5		43/20 (36)	(18)
	17 mo. later: 7/24/53	200	96	4.4		33/15 (21)	(18)
	44 mo. later: 10/ 6/55	180	96	4.6	17/5 (12)	60/40 (47)	50/35 (40)
	2nd C.: 11/25/55						
5 Female 28	before C.: 11/19/51	170	91	5.2		48/22 (30)	(28)
	1st C.: 12/ 3/51						
	2nd C.: 9/ 7/56						
6 Female 30	before C.: 11/26/53	210	91	5.7	(12)	130/70 (90)	(35)
	1st C.: 1/22/54				Per operative pressures:		see Table III
	29 mo. later: 6/29/56	150	93	2.6	20/8	140/70 (100)	55/40 (50)
	2nd C.: 9/14/56						
	3 wk. later: 10/ 5/56	150	96	3.2	6/3 (4)	65/30 (45)	23/16 (18)

1st C., 2nd C., and before C. = first, second, and before commissurotomy, respectively. R.A. = right auricle; P.A. = pulmonary artery; C.P. = capillary pressure.

CASE MATERIAL

A recurrence of a syndrome of tight mitral stenosis occurring from 9 months up to 3 years after commissurotomy, and involving a second surgical procedure, was observed in 6 cases. These 6 cases were part of a series of 380 commissurotomies performed during the period from 1950 to 1956. The first group, consisting of 180 cases, was operated upon with digital fracture alone. In the second group, comprised of 200 cases (beginning in April, 1954), 95 per cent of the operations were completed by use of the dilatator.* All 6 cases to be discussed are part of the first group.

CASE 1.—This 21-year-old man was admitted to the Hôpital Lariboisière on March 18, 1952, complaining of shortness of breath since 15 years of age. There was no history of rheumatic or scarlet fever. Exercise tolerance was reduced to 600 meters walking on flat ground. During the past 6 years he had had several attacks of nocturnal, acute pulmonary edema and bouts of bronchitis in winter time. *Physical examination* revealed normal rhythm, and rumbling mid-diastolic murmur with accentuation of the first heart sound at the apex. *Fluoroscopy* revealed a moderate cardiac enlargement, with a slight bulging of the pulmonary conus, a moderately large left atrium, and large pulmonary arteries with increased lung hilus shadows. *Electrocardiogram* showed sinus rhythm, enlarged and high P_1 and P_2 waves. The QRS axis was $+80°$, and there was slight right ventricular hypertrophy. *Laboratory data* included normal sedimentation rate, blood fibrin 2.5 Gm. per liter, and total protein nitrogen 43 mg. per cent (Table II). *Hemodynamics*, on July 7, 1952, are shown in Table I.

First Operation.—(April 24, 1953.) The mitral leaflets were supple. The mitral area was just over 1 square centimeter. The stenosis was more marked on the antero-external commissure, which was somewhat calcified. There was no mitral regurgitation. The postoperative course was very progressive but improvement incomplete. Dyspnea on exertion almost disappeared, but not entirely. There was no more acute pulmonary edema. On fluoroscopy, the bulging of the pulmonary conus was less marked and the pulmonary fields were clearer. The electrocardiogram was unchanged. Results of postoperative catheterization on Dec. 14, 1953, are shown in Table I.

Almost 2½ years after commissurotomy, following some days of hard physical work, exertional dyspnea and acute edema reappeared very suddenly and were more severe than before the operation. On examination, the clinical signs, radiologic and electrical findings were the same as preoperatively. Laboratory data were normal as to sedimentation rate, blood fibrin, electrophoresis, and C reactive protein, but antistreptolysin units were up to 500 (Table II). A catheterization was performed on Jan. 3, 1956 (Table I).

Reoperation.—(Feb. 10, 1956.) The mitral area was smaller, less than 1 square centimeter. The valvular tissues were hardened, especially along the borders. The digital opening was very difficult, but with the instrument a total opening was completed without regurgitation. The postoperative course showed very fast improvement. The lung hilus shadows were cleared up. On the electrocardiogram, P waves returned toward normal, and the QRS axis was $+70°$. Laboratory data were normal (Table II).

CASE 2.—This 22-year-old woman was admitted to the Hôpital on June, 8, 1953, complaining of orthopnea, dyspnea on effort, and rare attacks of acute pulmonary edema, over a period of one year. At 17 years of age she had had acute rheumatism, and at 20, mitral stenosis was diagnosed. *Physical examination* showed normal rhythm, rumbling mid-diastolic murmur, with accentuation of the first heart sound at the apex and of the second sound at the pulmonary area. *Fluoroscopy* revealed a moderate cardiac enlargement with prominent pulmonary conus and pulmonary arteries, and increased lung hilus shadows. *Electrocardiogram* showed sinus rhythm,

*The dilatator was designed by the surgeon, Dr. Marceau Servelle.

enlarged and high P_1 and P_2 waves, and a QRS axis of +140°. There was marked right ventricular hypertrophy. *Laboratory data* gave a normal sedimentation rate, blood fibrin 2.75 Gm. per liter, and antistreptolysin units of 160 (Table II). The *hemodynamics*, on June 10, 1953, are given in Table I.

TABLE II

CASE SEX | AGE	COMMISSUROTOMIES AND DATES		SEDIMENTATION RATE 1 AND 2 HR.	TOTAL BLOOD FIBRIN (GM./1,000 CM.^{3})	ELECTROPHORESIS	ANTISTREPTOLYSIN (UNITS)
1		B 1 mo.	5–15	2.50	—	—
	1st C.	A 1 mo.	13–20	4.40	—	—
Male	April 1953	2 mo.	6–14	—	—	—
21	2nd C.	B 1 mo.	2–5	2.70	Normal	500
	Feb. 1956	A 1 mo.	3–11	3.10	Normal	500
2		B 1 mo.	2–5	2.75	Normal	—
	1st C.	A 15 days	20–40	3.90	With globulin slightly elevated	160
Female	July 1953	1 mo.	2–9	—		
22		B 1 mo.	2–3	2	—	—
	2nd C.	A 1 mo.	6–14	1.80	Normal	50
	Dec. 1955	4 mo.	2–9	3	Normal	125
3		B	—	—	—	—
	1st C.	A 1 mo.	20–40	—	—	—
Female	April 1951	4 mo.	43–67	—	—	—
		7 mo.	2–4	2.65	—	—
23		1 yr.	—	—	With globulin increased	100
		B 6 mo.	35–70	6	Normal	—
	2nd C.	A 15 days	56–105	6.60	Normal	50
	Dec. 1954	2 mo.	36–60	4.60	Normal	200
		4 mo.	8–16			
4	1st C.		—	—	—	—
Female	Feb. 1952					
		B 6 mo.	4–13	—	—	—
32		3 mo.	7–20	3.60	Normal	50
		2 mo.	30–46	4.80	—	—
		1 mo.	12–22	—	With globulin increased	200
	2nd C.	A 1 mo.	14–38	4.60	With globulin normal	50
	Nov. 1955	2 mo.	4–12	—	—	—
6		B 2 mo.	22–40	3.70	—	—
		1 mo.	12–29	—	Normal	—
Female		10 days	6–20	—	—	—
	1st C.	A 1 mo.	70–90	4.20	—	—
30	Jan. 1954	45 days	12–24	—	—	—
		2 mo.	35–60	—	—	—
		3 mo.	10–20	—	Normal	—
		B 3 mo.	2–4	3.5	Normal	50
		2 mo.	28–59	6.40	—	200
		1 mo.	12–26	—	—	—
	2nd C.	A 15 days	39–76	5.40	With globulin increased	125
	Sept. 1956	1 mo.	9–10	—	—	200

B = before; A = after; C. = commissurotomy.

First Operation.—(July 7, 1953.) The mitral leaflets were supple; the mitral area was less than 1 square centimeter. The digital opening was satisfactory. There was no mitral regurgitation. Postoperative course showed clinical improvement for 1 year. In June 1954, an episode of infection of the respiratory tract was followed by a reappearance of dyspnea. Catheterization was performed on Oct. 7, 1954 (Table I).

During the next 18 months there was a deterioration of the situation, with a loss of weight of 10 kilos, and an accentuation of respiratory distress. Examination gave the same findings as before the operation. A catheterization was performed Dec. 3, 1955 (Table I). Laboratory data were normal (Table II).

Reoperation.—(Dec. 17, 1955.) The mitral valves were hardened but without calcifications. The mitral area was smaller, less than 1 square centimeter. The digital fracture was difficult, but with the instrument a bilateral commissurotomy was completed up to the mitral ring without regurgitation. The postoperative course showed very fast clinical improvement with no more dyspneic troubles. The diastolic rumble disappeared but a faint systolic murmur was heard at the apex. The electrocardiogram shifted toward the normal. Laboratory data were normal (Table II).

CASE 3.—This 23-year-old woman was admitted to the Hôpital on Feb. 12, 1951, complaining of shortness of breath since the age of 7 years. There was orthopnea and severe dyspnea on effort. There was no history of rheumatic or scarlet fever. *Physical examination* revealed normal rhythm, and loud diastolic rumble with marked accentuation of the first heart sound at the apex. *Fluoroscopy* showed moderate cardiac enlargement with a slight bulging of the pulmonary conus, large left atrium, and no change of lung hilus shadows. *Electrocardiogram* indicated sinus rhythm, enlarged and high P_1 and P_2 waves, QRS axis $+70°$, and incomplete right bundle branch block. *Hemodynamics*, on March 14, 1951, are given in Table I.

First Operation.—(April 9, 1951.) The mitral valves were hardened, the mitral area was around 1 square centimeter. The opening of the valve was very difficult, but on the third attempt a rather good fracture of both commissures was obtained. Postoperative course was rather stormy, with several attacks of flutter, a postcommissurotomy syndrome with fever, joint pains, and alterations of biologic data (Table II). After several months of rest and treatment, a marked improvement was realized, but the dyspnea on effort was still present. Catheterization data on June 22, 1951, are given in Table I.

During 1953, the patient lost 6 kilos of weight and the symptoms reappeared, with several attacks of flutter and, later, a persistent auricular fibrillation accompanied by enlarged liver and clinical signs of cardiac failure. The radiologic and electrical signs remained unchanged. The laboratory data were modified (Table II).

Reoperation.—(Dec. 24, 1954.) The mitral tissues were hardened, especially along the borders. The mitral area was smaller, 0.5 square centimeter. The opening of the valve was difficult, but with the instrument a complete fracture was obtained. During the postoperative course there was no improvement. Auricular fibrillation persisted, with an enlarged heart and several attacks of rheumatic fever which were difficult to control.

CASE 4.—This 32-year-old woman was admitted to the Hôpital on Dec. 24, 1951, complaining of shortness of breath for a period of 10 years. It had become permanent, with attacks of acute pulmonary edema on slightest effort. She had a history of scarlet fever at the age of 12 years and rheumatic fever at 13. *Physical examination* indicated normal rhythm, slight aortic insufficiency, and loud diastolic rumble with accentuation of the first heart sound at the apex. *Fluoroscopy* showed moderate cardiac enlargement, with a large left atrium, a bulging of the pulmonary conus, and increased lung hilus shadows. *Electrocardiogram* revealed sinus rhythm, enlarged P_1 and P_2 waves, and a QRS axis of $+60°$. There was no right ventricular hypertrophy. *Laboratory data* were subnormal (Table II). *Hemodynamics*, on Jan. 11, 1952, are given in Table I.

First Operation.—(Feb. 1, 1952.) The mitral leaflets were supple. The mitral area was 1 square centimeter, with a small regurgitant jet. A satisfactory digital fracture of the commissures was performed without increased regurgitation. Postoperative course was very rapid with impressive improvement, except for persistent dyspnea on effort. The fluoroscopy findings were better; the electrocardiogram was unchanged. A catheterization (July 16, 1952) showed a partial return toward normal, which persisted (July 24, 1953, Table I). Normal activity was continued

for 3 years. In April 1955, a sudden attack of paroxysmal dyspnea was followed by all the preoperative symptoms, and particularly by several attacks of severe pulmonary edema. At the same time auricular fibrillation was noted with an accentuation of radiologic findings. A catheterization was performed on Oct. 6, 1955, which showed higher pressures than before the operation (Table I).

Reoperation.—The mitral tissues were hardened; the mitral area was smaller. Digital opening was very difficult, but with the instrument a good fracture was obtained on the external commissure and an incomplete one on the internal, very thick commissure. In the postoperative course, 8 months after the operation the symptoms had cleared up, with a persistent auricular fibrillation.

CASE 5.—This 28-year-old woman was admitted to the Hôpital on Nov. 10, 1951, with a complaint of severe dyspnea on effort, dating back 4 years to when she had her first attack of nocturnal pulmonary edema. She had a history of rheumatic fever at the age of 12 years, with recurrence every year up to age 20. *Physical examination* showed normal rhythm, and loud diastolic rumble with marked accentuation of the first heart sound at the apex. *Fluoroscopy* revealed moderate cardiac enlargement with a slight bulging of the pulmonary conus, and a large left atrium. *Electrocardiogram* showed sinus rhythm, a QRS axis of +80° and no right ventricular hypertrophy. *Hemodynamics*, on Nov. 19, 1951, are shown in Table I.

First Operation.—(Dec. 3, 1951.) The mitral area was around 1.5 square centimeters. The mitral valve was calcified all around the orifice. The digital commissurotomy was very difficult and an opening to two fingerbreadths was obtained. Postoperative course showed rather rapid improvement and normal activity, with disappearance of pulmonary edema. One year later, after a sore throat and bronchitis, there was a sudden return of pulmonary edema on effort. During 1955 and 1956, permanent orthopnea with severe physical incapacity and bouts of right ventricular failure developed. The patient refused a checkup and wanted an operation.

Reoperation.—(Sept. 7, 1956.) The mitral area was smaller, less than 0.5 square centimeter. A complete fracture of both commissures was obtained with the dilatator. In the postoperative course improvement was very abnormal and fast. The right ventricular failure disappeared, with no more pulmonary edema or diastolic rumble at the apex. The electrocardiogram was normal, with a QRS axis of +60°.

CASE 6.—This 28-year-old woman was admitted to the Hôpital on Nov. 23, 1953, complaining of shortness of breath of 4 years' duration. There was no history of rheumatic or scarlet fever. She had several attacks of acute pulmonary edema on effort and was increasingly dyspneic for a few stairsteps. Some weeks before she had had an attack of acute cardiac failure with fever, orthopnea, swelling of the ankles, and enlarged liver. *Physical examination* showed normal rhythm, rumbling mid-diastolic murmur with accentuation of the first heart sound at the apex, and loud second sound on the pulmonary area. *Fluoroscopy* revealed a moderate cardiac enlargement with a marked bulging of the pulmonary conus, large pulmonary arteries, and increased pulmonary vascularization. *Electrocardiogram* indicated sinus rhythm, enlarged and high P_1 and P_2 waves, QRS axis of +120°, and marked right ventricular hypertrophy. The horizontal vectorcardiogram was suggestive of extreme right ventricular strain. *Laboratory data* revealed that the sedimentation rate was for a while very rapid. Blood fibrin was normal (Table II). *Hemodynamics*, on Nov. 26, 1953, are shown in Table I.

First Operation.—(Jan. 22, 1954.) The mitral leaflets were supple and the mitral area was around 0.5 square centimeter. Large digital fracture of both commissures was accomplished. In the postoperative course there was rather rapid improvement, with disappearance of pulmonary edema on effort and orthopnea. There was still some shortness of breath on mild effort. Immediately after the operation some pains in the left shoulder were noticed, with a rapid sedimentation rate and a normal blood fibrin (Table II). In January, 1956, 2 years following commissurotomy, after an episode of fever, cough, and frothy sputum, severe dyspnea on effort reappeared. In June 1956, there was a slight attack of joint pains, with rapid sedimentation rate and higher blood fibrin (Table II). On examination, clinical signs and radiologic and electrical findings were the same as at the time of the preoperative checkup. A catheterization was performed on June 29, 1956 (Table I).

Reoperation.—(Sept. 14, 1956.) The mitral leaflets were still supple. The mitral area was about 1 square centimeter. The digital opening was 2 square centimeter; with the instrument the opening was completed up to the valvular ring. The postoperative course was a very abnormally rapid improvement. The diastolic rumble was no longer present, but there was a faint systolic murmur at the apex. The vectorcardiogram revealed sudden disappearance of the right ventricular strain. The catheterization, 3 weeks after the second operation (Oct. 5, 1956), showed a considerable drop of the pressure at rest (Table I). For a short while there was slight alteration of the laboratory data, but it quickly returned toward normal (Table II).

COMMENTS

To our 6 cases can be added 5 already published by various authors: Donzelot and associates,[4] Santy and co-workers,[9] McKusick,[8] Keyes and Lam,[7] and Gleen and Dineen.[5] The study of these 11 cases will permit consideration of the resealing of the valve, the limits of the syndrome which express it, and the data which make the diagnosis possible (Table III).

Frequency.—Actually, the recurrence of mitral stenosis seems rare, judged from a survey of the literature: 1 case out of 178 operations (Bailey); 1 case out of 120 (Keyes and Lam[7]); 1 case out of 160 (Santy[9]). For Wood the frequency is around 5 per cent of all cases. Out of our 380 commissurotomies we collected 6 cases. On the other hand, in a postoperative survey of 5 years, Glover and associates[6] have found no case of resealing of the valve out of 600 patients operated on.

However, those facts are not yet definitive; many late postoperative results remain insufficiently studied. It is possible that resealing of the valves may appear far more frequently. At the same time, a survey over a longer period of time will permit checking the value of the dilatator as to whether its use abolishes the recurrence of the mitral stenosis.

Age.—Almost every instance of resealing was observed in young patients under 30 years of age (8 cases out of 11).

The Physiopathologic Type of Stenosis.—Preoperatively, the circulation pressures were less. The more frequent finding was mitral stenosis with pure high capillary pressure (low pressure gradient between mean pulmonary and mean capillary pressure); but in 2 cases (Cases 2 and 6) there was a high pulmonary hypertension with a high pressure gradient between mean pulmonary and mean capillary pressure.

The First Operation Findings.—The anatomic condition of the valve varied. Usually, thickened and rigid leaflets were found, but sometimes they were supple (in 4 of our 6 cases). Rarely were calcified deposits noted. The mitral stenosis was always tight, except in 1 case where the mitral area was estimated to be 1.5 square centimeter.[5] A slight regurgitant systolic jet was found in 2 cases.[4]

The First Commissurotomy.—The initial commissurotomy was digital in every instance. The operative reports do not point out any technical difficulties greater than usual. The fracture of at least one commissure was made routinely, but sometimes the internal commissure was incompletely opened, sometimes both commissures. After all, if the fracture seemed satisfactory, as in most of the cases, with excellent and lasting results, the commissurotomy was never completed by a fracture of both commissures up to the mitral valve ring.

The Postoperative Follow-up Study.—

1. *Clinical signs:* As a rule, the evolution was made in two successive periods. During the first period the improvement was such as is usually observed after an efficient commissurotomy. There was no longer any paroxysmal edema or dyspnea on effort, but in some instances there was still some slight dyspneic bouts on effort. (Often it is a comparative estimation of the functional postoperative troubles which permits the patient to appreciate the incomplete improvement due to the first operation.) The duration of the functional improvement was very short in the case of Santy and colleagues; it was negligible in the case of Donzelot and co-workers; but in all other cases the improvement lasted longer: up to 1 year in 4 cases, 2 years in 4 cases, and 3 years in 1 case. In our cases a

TABLE III. ELEVEN CASES OF RECURRENCE OF MITRAL STENOSIS

CASES	AGE	VALVES	COMMISSUROTOMY	HEMODYNAMICS L.A. OR C.P. (MM. Hg)	DURATION OF IMPROVEMENT	VERIFICATION
Soulié & Colleagues 1	20	Supple	Opening to 2 sq. cm.	B (26) A (12)	27 mo.	Reoperation (2½ yr.)
2	22	Supple	Enlarged to 2 fingerbreadths	—	13 mo.	Reoperation (2½ yr.)
3	23	Thickened	Enlarged to 2 fingerbreadths	B (22) A (15)	1 yr.	Reoperation (3½ yr.)
4	35	Supple	Enlarged to 2 fingerbreadths	B (28) A (18)	3 yr.	Reoperation (4 yr.)
5	28	Partial calcification	Enlarged to 2 fingerbreadths	—	1 yr.	Reoperation (4½ yr.)
6	30	Supple	Opening of both commissures	L.A.—B (48-34) A (24-14)	2 yr.	Reoperation (2½ yr.)
Gleen & Dineen	39	Thickened	Fracture of anterolateral commissure	Postoperative C.P. (12)	2 yr.	Reoperation (3 yr.)
Donzelot & Colleagues	29	Sclerous	Good on anterolateral commissure	—	15 days	Autopsy (1 mo.)
Santy & Colleagues	26	Sclerous	Good on anterolateral commissure	—	2 mo.	Reoperation (18 mo.)
Keyes & Colleagues	29	Calcified	Enlarged to 2 fingerbreadths	L.A.—B (25-14) A (12-9)	2 yr.	Reoperation (2½ yr.)
McKusick	42	Sclerous	Good on anterolateral	B (32) A (21)	1 yr.	Autopsy (4½ yr.)

L.A. = left auricle; C.P. = capillary pressure; B = before commissurotomy; A = after commissurotomy.

For the first 6 cases (personal patients) the hemodynamic data are given in the table. For the other cases, the mean pulmonary pressure and the mean capillary pressure preoperatively are, respectively: Keyes and Lam: 52 and 35 mm. Hg; McKusick: 63 and 32 mm. Hg; and Gleen and Dineen: 38 and 28 mm. Hg.

peculiar fact was the rather sudden revival of the previous preoperative troubles: after acute nocturnal pulmonary edema in Cases 1 and 4; after removal of the appendix and a common pulmonary infection in Case 3; within a few days after bronchitis in Case 6.

2. *Hemodynamic controls:* The postoperative hemodynamic study also revealed the same two successive periods of evolution. The hemodynamic investigation showed immediately either a preoperative drop of pressure in the left auricle (in the case of Keyes and Lam, and our Case 6) or a postoperative clear drop of the capillary and pulmonary artery pressure (in the cases of McKusick and Gleen and Dineen, and 3 of our cases). But there was only a partial improvement in 4 cases. After the clinical relapse, the pressures rose again to an even higher level than before the operation (in the case of Keyes and Lam, and 3 of our cases).

The Findings at Reoperation.—Some interesting facts appear when we analyze the operative data:

1. In all the published cases there was a reconstitution of mitral stenosis. In 2 out of 3 autopsied cases a linear healing existed where the fracture had been made previously (the third case will be discussed later).

2. The mitral stenosis was almost regularly found to be tighter than at the first operation; 5 of our cases demonstrated this point quite conclusively.

3. In 4 of our 6 cases, the mitral leaflets were supple at the first operation, and in one of those cases (Case 6) the mitral leaflets were still supple at the second operation, with the mitral area reduced a little. But there were no similar findings in the other cases in which there was a profound change of the mitral apparatus along with the recurrence of the stenosis. The leaflets were no longer supple, but hardened and thickened, and the contour of the mitral orifice was irregular. Santy himself noticed the "harder" consistency of the stenosed mitral valve, and Gleen and Dineen noted important transformations of the valve itself.[5]

4. These important changes of the mitral valvular apparatus accompanying the clinical recurrence of the stenosis are of great practical interest. The second operative commissurotomy is more difficult; the digital fracture is harder to accomplish and more limited; usually there is no possibility to open the stenosis as fully as at the first operation. The surgeon must use the dilatating instrument in order to obtain a complete, bilateral fracture.

DISCUSSION OF THE BASIC FACTORS IN THE DEVELOPMENT OF RECURRING STENOSIS

Because of the rarity of such data, the underlying causes for the reconstitution of a hemodynamic and clinical syndrome of tight mitral stenosis following initially successful surgery are not well known.

1. *In most of the cases, the cause seems to be a refusion of the mitral commissures.* The post-mortem examinations of a few cases and the findings at the reoperation show it with evidence in 10 cases.

Different mechanisms may preside over the true re-establishment of stenosis:

a. The role of an evolutionary rheumatic activity, and its resurgence due to the operative procedure, must be discussed in the light of McKusick's case and 3 of our cases. In Case 6, immediately after the first operation and 2½ months

after the second one, there was noticed to be transient joint pains with some temperature, increased sedimentation rate, and increased blood fibrin, with a normal antistreptolysin rate. Such episodes suggest an uncontrolled rheumatic activity, but it lasted for too short a time and had too discontinuous a character to be held with certainty as the cause of the recurrence of the mitral stenosis. In Case 4, the reappearance of symptoms 3 years after the first operation were coincident with the setup of a persistent auricular fibrillation; the biologic data showed slight disturbance. Case 3 was remarkable because of a rheumatic attack due to the commissurotomy. There was no history of rheumatic fever, but 5 weeks after the operation a sore throat, joint pains, fever, and increased sedimentation rate were noted. During the following months 4 similar attacks occurred. The following year, during a pregnancy, a transient auricular fibrillation developed, with attacks, later, of auricular flutter and persistent auricular fibrillation succeeding each other. The heart became enlarged and the biologic data indicated disturbance.

Finally, if the importance of the rheumatic activity was dubious in Cases 4 and 6, it was clear-cut in Case 3. It was likewise in McKusick's case in which symptoms of rheumatic activity were evident for 3 years.

b. Quite different are Cases 1, 2, 5, where there was no biologic or clinical rheumatic activity before or after the operation. In the case of Santy and that of Keyes and Lam no joint pain or suspicious fever were noticed. A nonspecific mechanism seemed to be patent in those cases. Without any revival of rheumatic activity, the digital fracture provoked in some patients a reaction of sclerous scarring capable of altering the valves, which became thick and again shrank the mitral orifice within a few months, perhaps within a few weeks, making it narrower than before (except in one case where the leaflets were supple and the valves less tightly resealed than noted at the first operation). This nonspecific, nonrheumatic mechanism may be dependent upon the special capacity of a particular area to react with a diffuse sclerous scarring. (One knows that the average time for development of mitral stenosis is 5 years, but that it can be far shorter.) On the other hand, it is very well established that continuing hemodynamic disturbances are very highly favorable to changing tissues. Might remaining hypertension in the left atrium and pulmonary veins segment of the lesser circulation play a part?

c. To those facts it is necessary to add cases in which a local process of thrombosis had been noted; the histologic data of the case of Donzelot and associates shows that the progressive resealing scar of the valves is due to an organized local clotting.

The mechanism postulated by Margaray[7b] in the installation of a mitral stenosis deserves to be recalled here; the author believes that on the site of a very small injury made by a rheumatic process frost deposits of fibrin and platelets appear forming a fibrous structure. Such facts induce some authors to propose a systematic anticoagulant therapy during the 2 months following a commissurotomy.[3] This point of view seems especially applicable in cases where an unpaired mitral valve has been fractured incompletely and with difficulty and is able to initiate a continuing inflammatory process.

Finally, the refusion of the valve is made through the medium of two different mechanisms: rheumatic activity, and nonspecific.

The respective frequency of the two mechanisms is difficult to appreciate for it is often difficult to prove a cardiovalvular rheumatic activity and to explain the true consequences of resurgence of an inflammatory process. We know the usual lack of resealing of the valves after the "postcommissurotomy" syndrome, even in cases of long and severe attack, without the possibility of discussing the effect of a therapy with corticoid hormones. In other respects, in the reported cases it is striking to note the lack of the localization of the rheumatic activity to one or the other valves of the heart.[3,11]

The study of the 10 cases, with no case of auricular tissue biopsy, points out that a revealed relapse of rheumatic cardiac activity is not the usual, or even the most frequent, cause of the recurrence of a tight mitral stenosis; it is true in 3 cases, dubious in 2 cases, and not involved at all in 5 cases.

2. *The recurrence of the mitral obstruction is not inevitably due to the refusion of the mitral commissures.* The results of the first operation are but a still more accentuated alteration, and a distortion of the valve leads to a secondary stenosis of the mitral area. Two cases quoted by Gleen and Dineen[5] suggest this possibility. The same authors report a case where the mitral opening, more eccentric, was located in the already fractured anterior commissure; the valves became rigid with calcium deposits and a restenosis was built up in the medium zone of the valve, to the detriment of the posterior commissure which had not been fractured at the time of the first operation. Therefore, following an incomplete bilateral commissurotomy, and although one commissure had been fractured, the development of rheumatic activity was able to worsen the earlier lesions so as to create a new mitral barrier.

3. *Whatever is the cause, the recurrence of a tight mitral stenosis is noticed only after an incomplete commissurotomy.* The published cases until now are lacking in instances of dilatation with an instrument and of complete fracture of both commissures. That notion supports the opinion of Brock,[1] for whom the reconstitution of a mitral stenosis is unlikely if, with a complete severing of the "critical zones," a total mobilization of the valves is obtained. From this point of view the use of an instrument (dilatator) is a decided improvement over the earlier digital commissurotomy. With the instrument a far larger opening than the digital one can be gained, always facilitating arrival up to the mitral ring, and fracturing at least one of the commissures, frequently both. With this technique one can expect to keep the patients from having a recurrence of mitral stenosis.

CRITERIA FOR DIAGNOSIS

During a follow-up survey, the exact succession of regression and revival of the disorders was the chief test for the diagnosis of the recurrence of mitral stenosis.

1. The functional improvement must be clear-cut, with the disappearance of pulmonary edema and dyspnea on effort; it must be durable also. As a rule, a period of some months is necessary for a resealing of the commissures, or at

least for the appearance of a clinical syndrome of the recurring mitral stenosis. The intermediate period usually lasts from 1 to 2 years, sometimes 3 years or more.

2. The control of the pressures of the pulmonary circulation shows, as does the clinical study, the same evolution in two periods: first it brings out either the preoperative fall of pressure in the left atrium or the drop of the capillary pressure during the following months; later, with the renewal of symptoms, the pressures rise again, sometimes higher than before the operation.

If the clinical data give a clue, they could not give, however, a secure diagnosis without the hemodynamic findings. This conclusion is supported from another point of view by infrequent but difficult cases where the postoperative hemodynamic findings, especially abnormal ones, were due to a postoperative significant mitral regurgitation.

CONCLUSIONS

The recognized cases of recurrence of mitral stenosis are due to a commissurotomy efficient from the clinical and hemodynamic results but inefficient from the anatomic standpoint (incomplete opening up to the mitral ring).

SUMMARY

1. Six cases of unquestionable re-establishment of tight mitral stenosis involving a second operation are reported; 5 cases already published by other authors are reviewed.

2. The most important point which marks the recurrence of the stenosis is an evolution of clinical and hemodynamic signs within two periods: (a) a clear-cut regression of the symptoms which last from 1 to 3 years, and (b) a recurrence of the symptoms, which frequently appear abruptly, with an increase of the lesser circulatory pressures, so that a true syndrome of recurrence of tight mitral stenosis can be depicted.

3. The parallel evolution of clinical and hemodynamic signs must be checked upon, because these signs permit the settling of the outline of this problem in making the differential diagnosis with other conditions capable of affecting the future of operated patients.

4. An incomplete digital fracture and unsatisfactory mobilization of the valves seem to be the first condition for recurrent obstruction of the mitral valve. The mitral barrier is rebuilt most frequently from a remanifestation of the valvular lesions, due either to an acute or low-grade rheumatic activity or more often to a sclerous scarring of nonspecific process.

This study points out the improved value of fracture of the valves by instrument and the possible help and usefulness of an anti-inflammatory and anticoagulant treatment.

ADDENDUM

Since the writing of this paper, we have had the opportunity (1) to collect 3 more cases of the recurrence of tight mitral stenosis with reoperation similar to the 6 cases presented here, and (2) to look over the current literature and checkups. The report of L. B. Ellis and D. E. Harken[13] states that "Evidence will be presented that significant refusion of the valves has occurred rarely within the period of observation." C. P. Bailey and H. Goldberg[14] have reported that "We now

can confirm in our own operation series indubitable re-establishment of stenosis in patients who have undergone at least an apparently reasonably adequate commissurotomy; in 6 patients autopsy evidence is available; in 11 others reoperations and hence digital re-examination of the valve by the original operating surgeon has seemed to offer sufficient proof of the development of such recurrent stenosis."

REFERENCES

1. Brock, R. C.: Brit. Heart J. **14**:489, 1952.
2. Carlotti, J., Soulié, P., Joly, F., and Sicot, J. R.: Etude hémodynamique postopératoire du rétrécissement mitral (56 cas). Report of the Second World Congress of Cardiology, Washington, Sept. 1954.
3. Coblentz, B., Hillemand, R., and Lenègre, J.: Arch. mal. coeur **49**:535, 1956.
4. Donzelot, E., Dubost, C., Heim de Balsac, R., Métianu, C., and Guillemot, R.: Arch. mal. coeur **46**:300, 1953.
5. Gleen, F., and Dineen, P.: Ann. Surg. **3**:405, 1956.
6. Glover, R. P., Davila, J. C., O'Neill, T. J. E., and Janton, O. H.: Circulation **11**:14, 1955.
7. Keyes, J. W., and Lam, G. R.: J.A.M.A. **155**:247, 1955.

7b. Magaray, F. R.: Brit. Heart J. **1**:856, 1951.

8. McKusick, V. A.: A.M.A. Arch. Int. Med. **95**:557, 1955.
9. Santy, P., Froment, R., Gallavardin, L., and Tolot, F.: Arch. mal. coeur **47**:615, 1954.
10. Soulié, P., Joly, F., Carlotti, J., Voci, G., and Servelle, M.: Traitement du rétrécissement mitral par commissurotomie. Indications et résultats post-opératoires (Etude hémodynamique). Report of the First European Congress of Cardiology, London, Sept. 1952.
11. Soulié, P., Bouvrain, Y., Fortin, P., DiMatteo, J., and Tricot, R.: Arch. mal. coeur **47**:49, 1954.
12. Soulié, P., Joly, F., Carlotti, J., and Sicot, J. R.: Arch. mal. coeur **49**:729, 1956.
13. Ellis, L. B., and Harken, D. E.: Circulation **14**:931, 1956.
14. Bailey, C. P., and Goldberg, H.: Circulation **14**:907, 1956.

THE ELECTROCARDIOGRAPHIC SYNDROME OF SHORT P-R INTERVAL AND BROAD QRS COMPLEXES

A Clinical Study of 80 Cases

Milton R. Hejtmancik, M.D., and George R. Herrmann, M.D.

Galveston, Tex.

FOR nearly 3 decades, the peculiar electrocardiographic configuration of short P-R interval and prolonged QRS complexes has been a fascinating topic for cardiologists. Wilson[1] published the first case and Wedd[2] the second, but the comprehensive description by Wolff, Parkinson, and White[3] really introduced the subject. Many designations have been applied to the disorder: Wilson-Wolff-Parkinson-White syndrome; Wolff-Parkinson-White syndrome; false bundle branch block; anomalous atrioventricular conduction; accessory bundle syndrome (Holzmann and Scherf[4]); bundle of Kent syndrome (Wolferth and Wood[5]); pre-excitation (Öhnell[6]); accelerated A-V conduction (Prinzmetal[7]).

The diagnosis is entirely an electrocardiographic one and casual observation has often resulted in serious misinterpretation. The tracings characteristically show a short P-R interval (less than the normal A-V nodal time of 0.12 second), a slurred upstroke of the R waves (delta wave), and a proportionally prolonged QRS interval (0.10 second or more). However, even in well-established cases, the tracing does not always show the strikingly unusual configuration of the syndrome. It may be changed spontaneously, after exercise, by breathing, or by drugs, to a normal or pseudonormal pattern. Clinically, the condition is manifested only by a tendency to sudden attacks of supraventricular arrhythmias in many of the cases.

The cause of the peculiar electrocardiographic configuration is not known. The most acceptable theory of an aberrant atrioventricular pathway was presented by Holzmann and Scherf[4] and by Wolferth and Wood.[5] Such accessory atrioventricular connections have been found in patients with this syndrome, and were demonstrated by Kent[8] in animals, especially in rats. Experimental short circuits were devised by Butterworth and Poindexter,[9] and applied to hearts with the production of characteristic Wilson-Wolff-Parkinson-White (WW-PW) electrocardiograms. Sodi-Pallares and associates[10] demonstrated two specific irritable points in the right septal mass, either one of which they felt might be stimulated by electrotonic diffusion of the supraventricular impulse. Segers and associates[11] reported a case of the syndrome with post-mortem demonstration of a neuromuscular bundle ending in such a portion on the septum. Prinzmetal and his co-workers[7] have maintained that the cause is an impairment of

From the Cardiovascular Service, University of Texas School of Medicine, Galveston, Tex.
Supported in part by the H. H. Weinert Fund for Cardiovascular Research.
Received for publication May 29, 1957.

nodal function, with resulting abolition of the normal delay in a certain part of the conduction system and thus pre-excitation of a corresponding ventricular area.

Although several hundred papers have appeared on this subject, few reports have dealt with clinical evaluation of a large number of cases. The more extensive analyses include studies of 11 cases by Wolff, Parkinson, and White[3]; 52 cases by Wolff and White[12]; 70 cases by Öhnell[6]; 65 cases by Willius and Carryer[13]; and 19 cases by Hunter, Papp, and Parkinson.[14] More such reports are desirable, in order to evaluate better this disorder of conduction: its etiology and incidence, the distribution of cases, the frequency and therapy of arrhythmias, and the prognosis.

We have surveyed from a clinical and electrocardiographic standpoint the records of all cases of the WWPW syndrome studied at the University of Texas Medical Branch in the past 25 years. Only those cases showing diagnostic findings in at least one tracing are included. Questionable cases, such as those with only short P-R interval and no clear-cut QRS changes, were omitted from the study. One of the authors was personally familiar with each of the cases. The results of this analysis provide an adequate general summation of the WWPW syndrome.

THE CLINICAL MATERIAL

A total of 80 hospitalized and clinic patients were found to fulfill our rigid criteria for a diagnosis of the WWPW syndrome. These were selected from an electrocardiographic file of 55,000 patients, and thus present an incidence of 0.15 per cent, or 1.5 in 1,000 patients. This compares roughly with the finding of 6 WWPW patients in 5,000 aviators reported by Manning,[15] and the 2 in 1,000 by Packard and associates.[16] It is higher than the frequency of 0.056 per cent calculated by Öhnell.[6]

The age and sex distributions are listed in Table I, the age recorded being that at the time the patient was last seen. There is a wide age range from 9½ months to 82 years. Although the highest age incidence is in the third and fourth decades, there are many cases in the young and in the old age groups. The incidence in the older age groups is lower than in the series of Willius and Carryer,[13] who found the greatest number of their cases in the fifth decade and only 38.5 per cent less than 40 years of age.

TABLE I. AGE AND SEX DISTRIBUTION

AGE IN YEARS	1-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	TOTAL
Males	3	4	10	11	6	7	6	0	1	48
Females	5	1	4	6	5	2	7	2	0	32
Totals	8	5	14	17	11	9	13	2	1	80

There is a predominance of males (60 per cent), corresponding roughly to the 70 per cent found by Wolff and White,[12] 64 per cent by Öhnell,[6] and 54 per cent by Willius and Carryer.[13] Although an increased incidence in the male is mentioned in most reports, this finding has not been noted in the experience of Wood.[17]

There were 74 white and 6 Negro patients. Since about one third of the patients in this institution are Negro, there is in this series a surprisingly low incidence of the disorder in this race. No mention has been made in the literature of white racial predisposition to the WWPW configuration.

ASSOCIATED DIAGNOSIS

Each patient had a complete clinical and laboratory examination to determine the underlying cardiac status. The cardiac diagnoses are listed in Table II. Forty-eight (60 per cent) of the patients had no evidence of organic heart disease. This is less than the 70.8 per cent reported by Willius and Carryer.[13] Most of the patients with heart disease were in the age group over 40 years, and 19 had coronary heart disease.

Seven patients had clinical evidences of acute myocardial infarction, in 6 of whom the QRS changes of muscle necrosis were obscured by the WWPW configuration. In 1 case the infarction was localized anteroseptally and in 2 posteriorly on the basis of evolutionary ST-T wave changes.

TABLE II. UNDERLYING CARDIAC STATUS

TYPE HEART DISEASE	NUMBER OF PATIENTS
None	48
Coronary (ischemic)	16
Coronary and hypertensive	3
Hypertensive	3
Congenital	6
Rheumatic	2
Acromegaly	1
Postpartal	1
Total	80

TABLE III. ASSOCIATED NONCARDIAC DIAGNOSES

NO ORGANIC HEART DISEASE (48 PATIENTS)		NUMBER OF PATIENTS
Psychiatric Conditions		16
Schizophrenia	7	
Anxiety Neurosis	2	
Alcoholism	2	
Opiate Addiction	2	
Depression	1	
Hysteria	1	
Psychopathy	1	1
Gastric Ulcer		1
Trigeminal Neuralgia		1
Benign Prostatic Hypertrophy		1
Gynecomastia		1
Pemphigus		21
ORGANIC HEART DISEASE (32 PATIENTS)		
Psychiatric Conditions		5
Alcoholism	2	
Schizophrenia	1	
Bromidism	1	
Anxiety Neurosis	1	
Carcinoma		2
Hernia		1
Gangrene (leg)		1
		9

In the others the process could not be established with certainty by the ECG, although the clinical manifestations clearly indicated the diagnosis. Only 1 case showed periods of normal atrioventricular excitation by which the ECG diagnosis of infarction could be established, in contrast to 4 such patients reported by Wolff and Richman.[18]

The 6 patients with congenital heart disease were all under 20 years of age. Four patients were observed to show the WWPW configuration at ages below 4 years. All of these had organic heart disease, the diagnoses being congenital fibroelastosis, transposition of the great vessels, interventricular septal defect, and Ebstein's anomaly. The latter has been found frequently associated with the syndrome by Sodi-Pallares.[19]

Thirty patients were admitted for evaluation with a primary diagnosis unrelated to the circulatory system. Table III presents an analysis of these patients, in whom the WWPW syndrome was diagnosed in the course of routine electrocardiographic study. Of 21 such patients with no evidence of heart disease, 16 were admitted and treated on the psychiatric service. Of 9 additional patients in whom organic heart disease was also diagnosed, 5 were on the psychiatric service. Thus, the total number of psychiatric patients manifesting this syndrome was 21 (26 per cent), an unusually high incidence which has not been observed previously. Eight of the patients had schizophrenia, while the remainder had a variety of psychiatric conditions.

This unusually high proportion of psychiatric patients is, no doubt, in part related to the presence of a large psychiatric service in the University of Texas Hospitals. However, it is difficult to explain the incidence entirely on this basis, since other services, such as surgery, were not represented by a proportionate number of patients. Four patients had multiple electroshock treatments, and 3 patients had courses of deep insulin therapy. All tolerated the procedures well. In 2 patients the electroshock therapy was monitored by a continuous electrocardiogram. The only significant changes were brief runs of paroxysmal atrial tachycardia in 1 patient, which ceased spontaneously. This was the only patient who had manifested symptoms of rapid heart action prior to the specific psychiatric treatment.

Three patients were on the surgical service, and had surgical procedures without complicating arrhythmias. Only 1 of these had a history of recurrent rapid heart action.

TABLE IV. ANALYSIS OF ECG FINDINGS

P-R Interval	0.07	0.08	0.09	0.10	0.11	0.12	0.13					
Number of Cases	2	12	7	31	11	14	3					
QRS Interval	0.08	0.09	0.10	0.11	0.12	0.13	0.14	0.16	0.18			
Number of Cases	4	14	11	10	21	10	7	2	1			
P-J Interval	0.17	0.18	0.19	0.20	0.21	0.22	0.23	0.24	0.25	0.26	0.27	0.28
Number of Cases	4	2	8	9	11	14	14	5	3	3	5	2

QRS Axis	−90° to −60°	−60° −30°	−30° 0°	0° +30°	+30° +60°	+60° +90°	+90° +120°
Number of Cases	3	9	19	14	11	22	2

ANALYSIS OF ECG FINDINGS

The majority of our patients had many electrocardiograms in the files; only 10 had a single tracing. Table IV summarizes the ECG findings in the most recent tracing on each of the 80 patients. Although each patient had 1 or more diagnostic records to be included in the series, the most recent tracing was not always diagnostic in each case. Spontaneous variability of the ECG is charac-

teristic of the syndrome, even to the point of normality. Fifteen of our patients had at some time in their course an ECG which would be considered within normal limits. However, in most of these, the knowledge of existence of the syndrome would make it possible to recognize slight residual upstroke slurring, indicating that the basic configuration was still present.

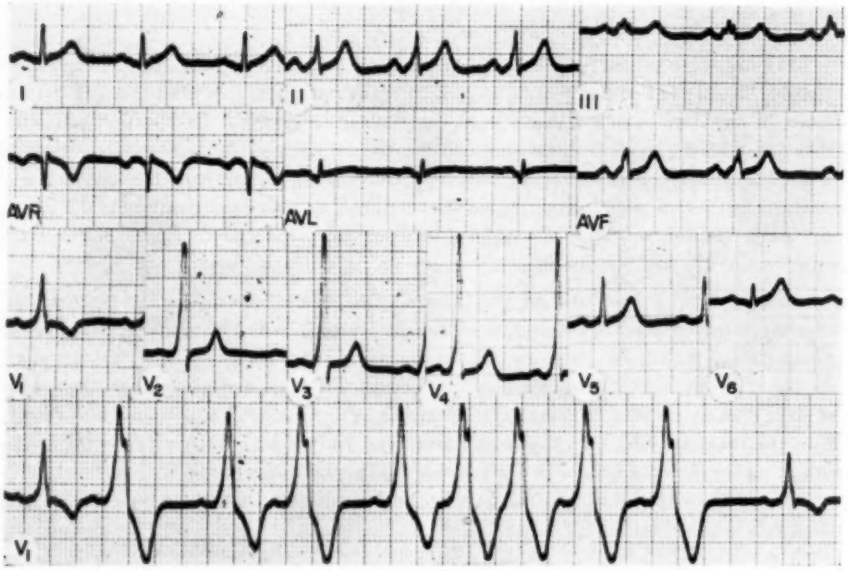


Fig. 1.—F. S., a 41-year-old white man, with no clinical evidences of organic heart disease but with recurrent paroxysms of atrial tachycardia. Limb leads show unusually broad, low delta waves. P-R is 0.13 sec., and thus not definitely shortened. QRS is 0.14 sec., and a concertina effect was demonstrated. A run of irregular atrial premature beats followed by more widened QRS complexes is present in the bottom strip (V_1).

Although the P-R is characteristically 0.12 second, or less, the most recent tracings in 3 cases showed the P-R to be over 0.12 second. Even in such cases, the syndrome should be strongly suspected if delta waves are found, and may be diagnosed if the concertina effect (Öhnell[6]) can be demonstrated. Differing QRS complexes in the same patient are considered to show this effect whenever this difference can be shown to be due to a variation in the time of onset. This effect in the WWPW syndrome has been demonstrated by Öhnell to be due to changes in the starting time of the component arriving via the bundle of His, the anomalous component, or both ventricular components. At times, carotid sinus pressure or such drugs as atropine or quinidine must be employed to demonstrate the concertina effect and establish the diagnosis. Changes in the arrival times of the ventricular depolarization waves via the normal or anomalous conduction pathway may produce striking variations in the QRS complex from beat to beat. An unusually broad, low-sloped delta wave as shown in Fig. 1 may be mistaken as part of the P-R segment. The unusually long P-R interval in this tracing was considered to be due to delayed conduction in both the normal and anomalous pathways.

The P-J interval (sum of P-R and QRS intervals) is generally not prolonged as a result of the broad QRS complexes, because of compensatory shortening of the P-R interval. It may actually be shortened as a result of the early ventricular excitation. In all of our cases except 7, the P-J interval was 0.26 second or less.

The QRS axes varied widely, from the extremes of marked left axis deviation (minus 90°) to right axis deviation (plus 120°). Thirty-one cases had a QRS axis to the left of 0°, but only 2 had a QRS axis to the right of plus 90°.

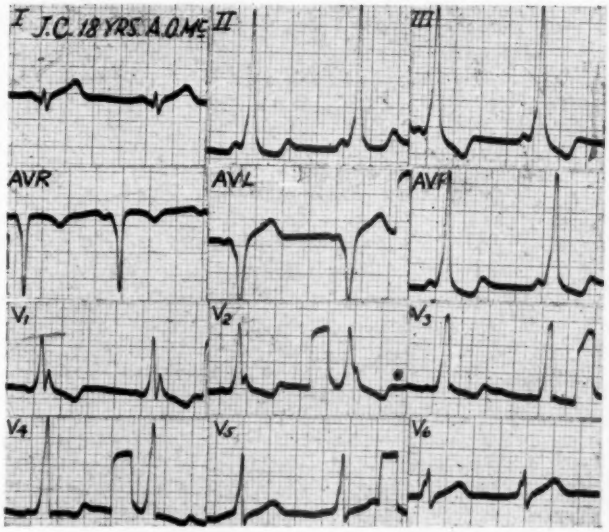


Fig. 2.—J. C., an 18-year-old white man, with recurrent paroxysms of atrial tachycardia. The Group A configuration simulates right bundle branch block.

Öhnell,[6] Burch,[20] and Sodi-Pallares[19] have divided the condition into various groups, basing their classifications on variations in the QRS complexes and form of the delta waves. We have chosen to utilize the most simple, that of the Wilson school,[21] which was extended by the intracardiac studies of Sodi-Pallares.[19] In Group A, the QRS axis is approximately plus 90°, there are no QS complexes in Leads II, III, and aV_F, and QRS complexes are positive on the anterior aspect of the chest and mainly negative on the posterior aspect (Fig. 2). This configuration simulates right bundle branch block. In Group B, the QRS axis is directed to the left, QS complexes are frequent in Leads II, III, and aV_F, and QRS complexes are positive in the left chest leads (Fig. 3). This group simulates left bundle branch block. According to these criteria there were in our series 13 patients in Group A and 48 patients in Group B. There were 16 other patients whose tracings would not fulfill the criteria of either group. Willius and Carryer[13] found an incidence of 40 per cent of "false left bundle branch block" and 6.2 per cent of "false right bundle branch block" in their series. The remainder of their cases did not exhibit the QRS-T reciprocal relationship of bundle branch block.

The effects of exercise, carotid sinus pressure, and various drugs on the electrocardiogram were occasionally evaluated. In 2 patients the Master exercise tolerance test was "positive" as judged by depressions of S–T segments after

exercise. However, more detailed evaluation of the postexercise tracings demonstrated slight variations in the QRS complexes which were considered responsible for the S-T segment shifts. In 3 other cases, the Master exercise tolerance test resulted in shortening of the QRS segment, and pseudonormalization. Carotid sinus pressure resulted in no apparent change in 5 tracings. In 1 case the P-R interval was shortened and QRS widened; in another there was an opposite

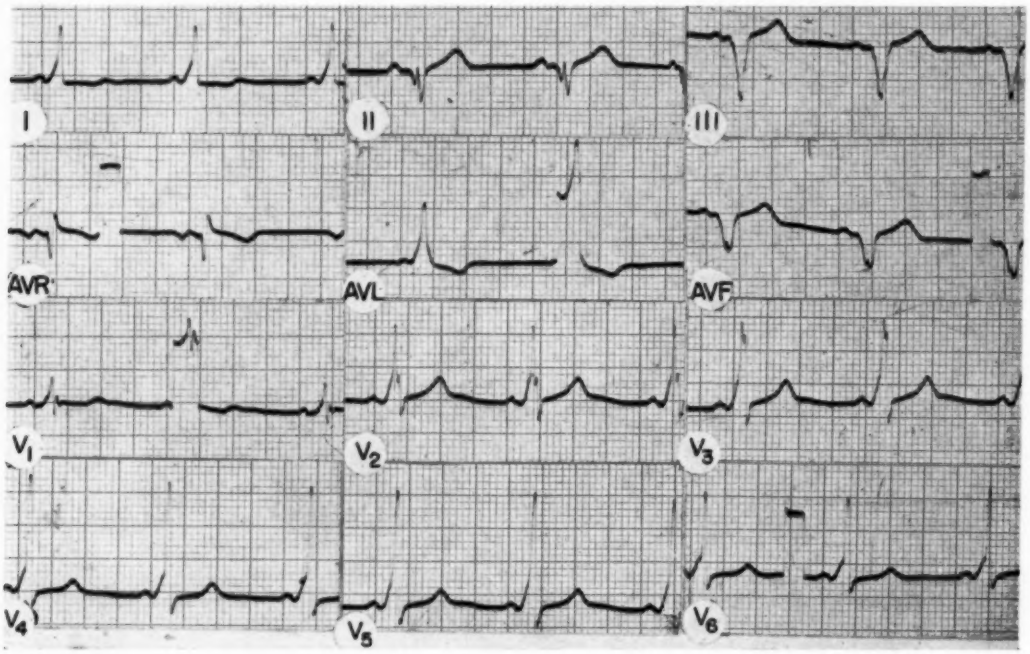


Fig. 3.—J. F. R., a 43-year-old white man, with no evidence of organic heart disease and no known rhythm disturbances. The Group B configuration simulates left bundle branch block.

effect with pseudonormalization of the tracing. Full atropinization, using 0.65 mg. of atropine intramuscularly, resulted in no ECG change in 3 patients, and pseudonormalization in 2. Prostigmin in 2 patients did not change the electrocardiogram. Quinidine, orally, resulted in narrowing of the QRS complex in 3 patients, but had no effect in 3 others. Such observations after administration of atropine and quinidine have been previously made by Littmann and Tarnower.[22]

ARRHYTHMIAS

Paroxysmal arrhythmias were clinically observed and usually recorded in 41 patients, or over half of our cases. Four other patients gave a history of paroxysmal rapid heart action, making a total of 45 patients (56 per cent) with known rhythm disturbances. This incidence is somewhat lower than the 70 per cent of Wolff and White[12] and Öhnell,[6] but closely approximates the 56.9 per cent reported by Willius and Carryer.[13] Our figure may be lower than the true incidence in this series because of possible inability of the many psychiatric patients to dis-

close their symptoms. However, since the WWPW syndrome is often an incidental finding without symptoms, the true incidence of arrhythmias complicating this disorder in the general population is probably below 50 per cent.

In Table V are listed the 42 arrhythmias clinically observed in 41 patients. There were 22 patients with paroxysmal atrial tachycardia, and 7 additional ones with a regular tachycardia presumed also to be atrial in origin. This would make a total of 29 patients with atrial tachycardia, representing 69 per cent of the arrhythmias. Two other patients had very frequent atrial premature contractions, in runs of 2 and 3. Atrial fibrillation occurred in 6 patients, and atrial flutter in 2. In 24 patients the arrhythmias were observed at least twice, with ventricular rates from 150 to 300 per minute.

TABLE V. OBSERVED PAROXYSMAL ARRHYTHMIAS

TYPE OF ARRHYTHMIA	NUMBER OF PATIENTS
Paroxysmal Atrial Tachycardia	22
Paroxysmal Atrial Fibrillation	6
Regular Tachycardia (undetermined)	7
Paroxysmal Atrial Flutter	2
Frequent Atrial Premature Beats	2
Frequent Ventricular Premature Beats	2
Ventricular Parasystolic Focus	1
Total	42

No sustained ventricular arrhythmia occurred in our cases. However, 2 patients had frequent ventricular premature contractions, in runs of 2. Another had a parasystolic ventricular focus which would for periods assume supremacy over the supraventricular cardiac rhythm, with periods of fusion beats.

In 14 cases arrhythmias occurred to complicate existing organic heart disease. These included 8 patients with paroxysmal atrial tachycardia, 2 with paroxysmal atrial fibrillation, and 2 with atrial flutter.

Seven of the patients had coronary heart disease, 2 with recent and 2 with old infarctions. Fig. 4 shows the tracing of such a patient who manifested atrial flutter as a complication of acute anterior myocardial infarction.

Records available of sustained arrhythmias (20) would not support previous observations that the rapid arrhythmias are nearly always accompanied by narrow QRS complexes (Table VI). Of 13 records of paroxysmal atrial tachycardia, there were 7 with narrow QRS complexes and 6 with broad QRS complexes simulating either ventricular tachycardia or atrial tachycardia with bundle branch block.[23] Of 5 records with paroxysmal atrial fibrillation, all had broad QRS complexes initially, but these usually became narrow before reversion with Pronestyl. One such patient presented paroxysmal atrial fibrillation and broad complexes in attacks in 1952, and paroxysmal atrial tachycardia and narrow complexes in 1956. One of the 2 patients with atrial flutter showed broad QRS complexes. The ventricular rates in the recorded cases were over 250 in 4 patients; 200 to 250 in 5; 150 to 200 in 8; and 140 to 150 in 3.

The main symptoms during the rapid heart action were described adequately in 45 patients, and are listed in Table VII. These varied widely, from mild subjective discomfort to cardiac pain, shock states, and loss of consciousness.

TABLE VI. ELECTROCARDIOGRAPHICALLY RECORDED SUSTAINED ARRHYTHMIAS

TYPE ARRHYTHMIA	NUMBER OF PATIENTS
Paroxysmal Atrial Tachycardia, with narrow QRS complexes (rates 250, 190, 150, 140, 210, 200, 150)	7
Paroxysmal Atrial Tachycardia, with broad QRS complexes (rates 230, 280, 145, 140, 180, 174)	6
Paroxysmal Atrial Fibrillation, with broad QRS complexes (rates 240, 300, 300, 260, 180)	5
Paroxysmal Atrial Flutter, with narrow QRS complexes (rate 165 per minute)	1
Paroxysmal Atrial Flutter, with broad QRS complexes (rate 157 per minute)	1
Total	20

TABLE VII. SYMPTOMS DURING PAROXYSMAL HEART ACTION IN 45 PATIENTS

SYMPTOM	NUMBER OF PATIENTS
Rapid heart action, regular	20
Rapid heart action, irregular	4
Palpitation	6
Dyspnea	8
Precordial pain	9
Dizziness	5
Blackouts	6
Weakness	5
Coldness	3
Warmth	2

TABLE VIII. AGE OF ONSET OF ARRHYTHMIAS AND NUMBER OF YEARS OF RECURRENCES IN 20 PATIENTS

AGE OF ONSET	YEARS OF RECURRENCE	AGE OF ONSET	YEARS OF RECURRENCE
1	32	16	11
2	3	17	4
5	55	18	1
5	21	20	14
8	14	23	5
10	27	27	5
10	6	38	3
11	1	39	1
12	21	43	10
15	5	50	10

Blackouts occurred in 6 patients, but none of these developed convulsions. Excessive emotional strain was the most frequent precipitating factor, but at times the paroxysms followed physical exertion and gastrointestinal disturbances. One patient developed atrial fibrillation with near loss of consciousness after a venesection of 500 c.c. of blood. Precordial pain was noted by 9 patients during paroxysms. One of these patients sustained an acute infarction during such an attack, and 5 others had coronary heart disease.

Twenty patients with recurrent arrhythmias were followed for periods of over 1 year. The age of onset of rapid heart action and the years over which they were observed are listed in Table VIII. In none of these patients did there develop evidences of organic heart disease. Thirteen of the patients noted onset of such recurrent arrhythmias before the age of 19, and 16 before the age of 29.

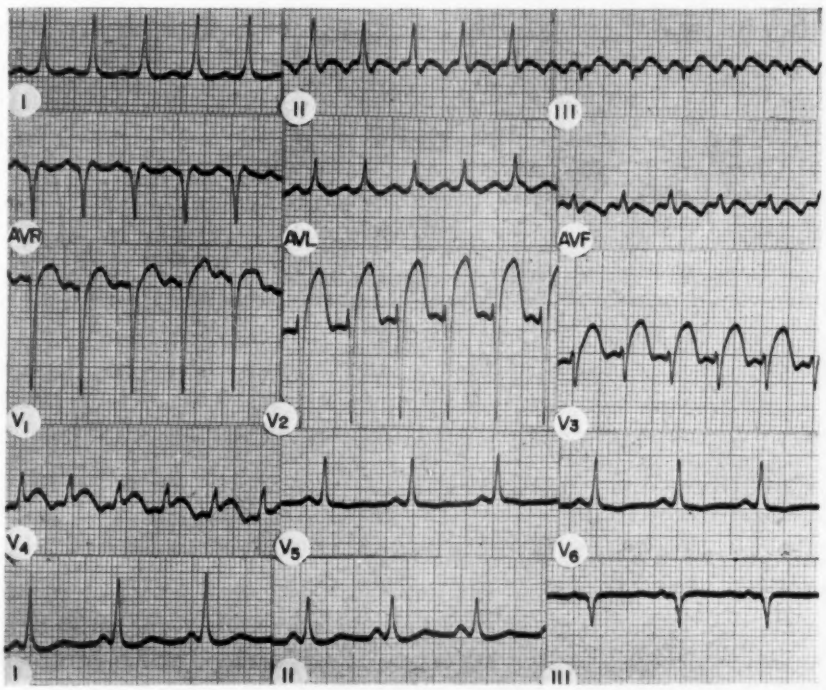


Fig. 4.—M. P., a 60-year-old white woman. There is atrial flutter with 2:1 block, with reversion to sinus rhythm in V_5. Precordial leads show ST-T changes compatible with acute anterior myocardial infarction. Subsequent tracings showed characteristic ST-T evolutionary changes, and a more definite WWPW configuration.

Two of the older patients in this series died suddenly, presumably as a result of a mechanism disorder. One of these was a 52-year-old man who had sustained recurrent episodes of paroxysmal atrial tachycardia, at rates of about 250 per minute, with narrow QRS complexes. This patient died suddenly, with no symptoms of coronary pain, and the post-mortem did not reveal acute coronary occlusion. The other patient, a 65-year-old white man, probably had coronary heart disease. He had experienced episodes of paroxysmal atrial fibrillation, and died during an unrecorded episode of rapid heart action. Necropsy was not

performed. Kimball and Burch[24] found 6 such deaths in the literature, apparently resulting from paroxysmal rhythmic disturbances, and added 2 others which they had observed. Another such case was reported by Silverman and Werner.[25]

REVERSION OF ARRHYTHMIAS

In most of the patients the arrhythmias reverted spontaneously or after the Valsalva maneuver, and no specific therapy was given. In 5 patients with paroxysmal atrial tachycardia there was reversion to sinus rhythm on carotid sinus pressure, and in an additional patient, reversion after intramuscular Prostigmin 0.5 mg. followed by carotid sinus pressure. In 2 cases of paroxysmal atrial tachycardia and 3 cases of paroxysmal atrial fibrillation, the arrhythmia was reverted by intravenous procaine amide in doses from 500 to 1,000 mg., with ECG control. Digitalis in combination with quinidine reverted the arrhythmia in 1 patient with paroxysmal atrial tachycardia, and in 2 patients with atrial flutter.

Langendorf and associates[26] demonstrated that in atrial fibrillation complicating the WWPW syndrome, quinidine depresses the conduction along the accessory pathway, while digitalis depresses the conduction along the A-V node and bundle of His. Thus, digitalis alone is ineffective in slowing the ventricular rate when administered to a WWPW patient with atrial fibrillation. Although the combined use of quinidine and digitalis has been suggested in such cases, the known effect of digitalis to increase ventricular irritability would seem to make its administration possibly hazardous. Quinidine would appear to be a suitable alternative in such atrial fibrillation, if Pronestyl therapy is unsuccessful.

Quinidine was employed as maintenance therapy after reversion in 10 patients. Dosage was small, usually 0.3 Gm. four times daily. Recurrences on this dosage were rare, but no definite conclusion regarding the prophylactic efficacy of quinidine can be drawn.

DISCUSSION

Although the WWPW syndrome is an infrequent ECG finding, occurring only in 1.5 per 1,000 patients in this series, all physicians who interpret electrocardiograms should be aware of its characteristics. At least 20 of the patients in this series were referred as having organic heart disease, when complete studies revealed no such evidence. Two of these patients were physicians who had markedly restricted their practices on the basis of mistaken diagnoses of coronary heart disease. Bundle branch block may be falsely diagnosed on the basis of the QRS changes, if the short P-R interval is not recognized. Secondary ST-T wave changes may be mistakenly interpreted as indicating myocardial ischemia. QS configuration in Lead I or in Leads II and III may lead to the erroneous diagnosis of myocardial infarction. Master exercise tolerance tests may be misjudged as positive on basis of S-T depressions after exertion.

A much higher proportion of our recorded arrhythmias showed broad QRS complexes than has been previously reported in the literature. Such tracings simulate ventricular tachycardia and fibrillation, and have been misdiagnosed and reported as such in previous publications. Electrocardiograms often are taken as the result of symptoms of paroxysmal heart action, and unfamiliarity with the

syndrome may result in an incorrect diagnosis of such a serious mechanism disorder. A patient known to have the WWPW syndrome who has episodes of rapid, regular heart action with broad QRS complexes can be assumed to have a supraventricular tachycardia with broad QRS complexes due to pre-excitation, unless an independent atrial pacemaker is found. Atrial fibrillation in such a patient usually results in a very rapid ventricular rate, over 200 per minute, which is rarely that high in atrial fibrillation with normal A-V conduction. Broad QRS complexes in such a patient may lead to the mistaken diagnosis of ventricular fibrillation. The generally fair condition of the patient, with palpable radial pulse, and obtainable blood pressure, should lead to the clinical exclusion of this diagnosis. We have made a presumptive diagnosis of WWPW syndrome in 2 patients whose initial electrocardiograms showed a ventricular rate of over 250 per minute, with broad, irregular QRS complexes, on the basis of the above clinical findings and characteristically high rate. Tracings after reversion showed this diagnosis to be correct.

However, in 3 of our cases, there were evidences of ventricular irritability, with parasystole in 1, and frequent ventricular premature beats in 2. Ventricular fibrillation is presumed to be the cause of death in the 2 patients who died as a result of a mechanism disorder. Unfortunately, tracings could not be taken at the time of death in these cases.

No therapy is indicated for the WWPW syndrome per se except the use of various maneuvers and drugs to establish the diagnosis or to alter the configuration in order to evaluate possible underlying disease. Reversions of complicating arrhythmias are usually spontaneous, but may require specific treatment. Prompt establishment of sinus rhythm is of particular importance in patients who have complicating organic heart disease and thus poorly tolerate the excessive ventricular rates. If the rhythm is regular, the usual carotid sinus pressure, Prostigmin, quinidine, or digitalization methods for termination of paroxysmal atrial tachycardia should be attempted. Digitalization may revert the paroxysmal supraventricular tachycardia to normal rhythm. However, digitalis is ineffective in slowing the high ventricular rate of atrial fibrillation found in this syndrome, as its principal action is on the normal atrioventricular conduction pathway. We have found Pronestyl intravenously with ECG control to be the most effective method for control in such patients, accomplishing reversion in all of our cases thus tried. Quinidine alone, or less preferably, quinidine and digitalis in combination, has been suggested as therapy for such arrhythmias. Combined digitalis and quinidine therapy was effective in our 2 patients with atrial flutter.

The unusually low incidence of cases in the Negro race, and the unusually high incidence in psychiatric patients should be further investigated by reports of other series. The problem of whether the psychiatric patients can be given electroshock and deep insulin therapy without increased risk should be studied also. In our experiences, there have been no serious complications with such therapy.

PROGNOSIS

The prognosis of the patient with ECG findings of the WWPW syndrome appears to be excellent if there has been no paroxysmal rhythm disturbance. It

must be somewhat guarded in the patient with episodes of rapid heart action, especially if there is underlying organic heart disease, which is unable to tolerate the rapid heart rates. In our experiences, a patient with this syndrome is unlikely to develop his initial attack of recurrent paroxysmal arrhythmia over the age of 30. Although all of the patients whom we have seen with sustained rapid heart action have shown a supraventricular arrhythmia, there were 2 deaths in elderly individuals from unrecorded arrhythmias. It is entirely possible that the impaired coronary circulation as a result of rapid atrial arrhythmias in these patients may have resulted in increased ventricular irritability, and thus superimposed ventricular fibrillation.

SUMMARY

1. An analysis is made of 80 patients with the syndrome of short P-R interval and broad QRS complexes, seen at the University of Texas Medical Branch.

2. Incidence of the syndrome is infrequent, being 1.5 per 1,000 patients.

3. Ages varied from 9½ months to 82 years, and 35 were over 40 years old. There was a slight predominance of males (60 per cent). Incidence in the Negro was infrequent.

4. Forty-eight patients (60 per cent) had no evidence of organic heart disease. Nineteen had coronary heart disease. Seven showed clinical evidences of acute myocardial infarction, but the ECG diagnosis was generally obscured by the broad QRS complexes.

5. There was a high incidence of psychiatric diagnoses (26 per cent). Seven patients subjected to electroshock and deep insulin shock therapies tolerated them well.

6. Successive tracings characteristically showed considerable variation. Even in otherwise diagnostic tracings, the P-R interval may occasionally exceed 0.12 second, but the concertina effect can be demonstrated.

7. There were 48 patients showing a QRS configuration of the Group B of Sodi-Pallares, and 13 patients of Group A. Sixteen had indeterminate patterns.

8. Effects of exercise, carotid sinus pressure, and various drugs on the ECG manifestations were confirmed. False positive Master exercise tolerance tests were demonstrated.

9. Forty-five patients (56 per cent) had arrhythmias, and we observed 29 with atrial tachycardia, 6 with atrial fibrillation, and 2 with atrial flutter. In 14 patients, the arrhythmias complicated organic heart disease.

10. Broad QRS complexes during the arrhythmias were more frequent than previously reported, and simulated ventricular tachycardia and ventricular fibrillation.

11. Two older patients died suddenly, presumably as a result of a mechanism disorder.

12. The usual methods of control of atrial tachycardia were found efficacious. Pronestyl intravenously under ECG control appeared to be the most effective method of reversion of atrial fibrillation.

REFERENCES

1. Wilson, F. N.: Arch. Int. Med. **16**:1008, 1915.
2. Wedd, A. M.: Arch. Int. Med. **27**:571, 1921.
3. Wolff, L., Parkinson, J., and White, P. D.: AM. HEART J. **5**:685, 1930.
4. Holzmann, M., and Scherf, D.: Ztschr. f. klin. Med. **121**:404, 1932.
5. Wolferth, C. C., and Wood., F. C.: AM. HEART J. **8**:297, 1933.
6. Öhnell, R. F.: Acta med. scandinav. (Supp.) **152**:1, 1944.
7. Prinzmetal, M., Kennamer, R., Corday, E., Osborne, J. A., Fields, J., and Smith, L. A.: Accelerated Conduction, New York, 1952, Grune & Stratton, Inc.
8. Kent, A. F. S.: Quart. J. Exper. Physiol. **7**:193, 1914.
9. Butterworth, J. S., and Poindexter, C. A.: Arch. Int. Med. **69**:437, 1942.
10. Sodi-Pallares, D., Soberón, J., Thomsen, P., Fishleder, B. L., and Estandía, A.: Arch. Inst. cardiol. México **18**:1, 1948.
11. Segers, M., Sanabria, T., Lequime, J., and Denolin, H.: Acta cardiol. **2**:21, 1947.
12. Wolff, L., and White, P. D.: Arch. Int. Med. **82**:446, 1948.
13. Willius, F. A., and Carryer, H. M.: Proc. Staff Meet. Mayo Clin. **21**:438, 1946.
14. Hunter, A., Papp, C., and Parkinson, J.: Brit. Heart J. **2**:107, 1940.
15. Manning, G. W.: Circulation **10**:401, 1954.
16. Packard, J. M., Graettinger, J. W., and Graybiel, A.: Circulation **10**:384, 1954.
17. Wood, P.: Diseases of the Heart and Circulation, Philadelphia, 1956, J. B. Lippincott Company.
18. Wolff, L., and Richman, J. L.: AM. HEART J. **45**:545, 1953.
19. Sodi-Pallares, D., and Calder, R. M.: New Bases of Electrocardiography, St. Louis, 1956, The C. V. Mosby Company.
20. Burch, G. E., and Kimball, J. L.: AM. HEART J. **32**:560, 1946.
21. Rosenbaum, F. F., Hecht, H. H., Wilson, F. N., and Johnston, F. D.: AM. HEART J. **29**:281, 1945.
22. Littmann, D., and Tarnower, H.: AM. HEART J. **32**:100, 1946.
23. Herrmann, G. R., Oates, J. R., Runge, T. M., and Hejtmancik, M. R.: AM. HEART J. **53**:254, 1957.
24. Kimball, J. L., and Burch G.: Ann. Int. Med. **27**:239, 1947.
25. Silverman, J. L., and Werner, M.: J. Pediat. **37**:765, 1950.
26. Langendorf, R., Lev, M., and Pick, R.: Acta cardiol. **7**:241, 1952.

FALSE RIGHT VENTRICULAR HYPERTROPHY PATTERN DUE TO WILSON'S CENTRAL TERMINAL ERROR

JOHN A. OSBORNE, M.D.,* AND GORDON E. DOWER, M.B.**

VANCOUVER, CANADA

A CURRENT tendency in electrocardiographic diagnosis is to attach less importance to the intrinsicoid deflection[1] and to deviation of the electrical axis[2] as criteria of right ventricular hypertrophy. This has resulted in more emphasis being placed on large R/S ratios in right precordial leads, regardless of the absolute size of the R waves. However, there is empirical evidence that small R waves in such leads may be misleading,[3] and estimations of the error in Wilson's central terminal[4] indicate that some of these may be due to artifact. The following case is an illustration of this.

CASE REPORT

T. H., a 20-year-old Army corporal of Japanese descent, had been well until July, 1955, when he developed a febrile illness associated with swelling and pain in the left elbow and right wrist and a subcutaneous nodule at the right elbow. A Grade 1 systolic murmur was heard at the apex. The P-R interval was prolonged and the erythrocyte sedimentation was 58 mm. in 1 hour. Chest films were normal. He was treated for acute rheumatic fever, responded well to salicylates, and returned to duty in September, 1955.

He was readmitted in January, 1956, because of a transient erythema, but no definite evidence of acute rheumatic fever was found. The apical systolic murmur was still present, however, and a faint, early diastolic murmur was heard by some. After 2 weeks he was discharged on prophylactic penicillin therapy, only to be readmitted 12 days later with acute pharyngitis and a papular rash over the shoulders and trunk. There were, otherwise, no new physical findings and uncertainty concerning the existence of a diastolic murmur persisted. Blood laboratory studies, which included estimation of the antistreptolysin titer and C-reactive protein were negative, as were throat cultures for pathogens. The ECG displayed a curious, spontaneous and abrupt variation of the P-R interval between 0.20 and 0.36 second, which was unaffected by drugs or exercise.

In March, 1956, he was referred to one of the authors for cardiac evaluation. General physical examination revealed straightening of the thoracic spine but otherwise confirmed the previous findings. Examination of the heart, supplemented by phonocardiography, revealed a normal first sound, a loud third sound and a loud pulmonary second sound. A systolic murmur of short duration and fairly low intensity was present at the apex. A faint sound was continuous throughout diastole but it was not characteristic of mitral stenosis. An opening snap was not present.

Received for publication June 17, 1957.

*From the Heart Station, Vancouver General Hospital, Vancouver, British Columbia, Canada.

**Department of Pharmacology, University of British Columbia; the G. F. Strong Memorial Fellow, British Columbia Heart Foundation, Vancouver.

In addition to the aberrant A-V conduction previously noted, the R/S ratio in V_1 was greater than unity, while in V_3R there was an R wave but no Q or S wave (Fig. 1). The QRS complexes in other leads were normal. Vectorcardiograms were taken with three different lead systems (Fig. 2, *A*, *B*, and *C*). The loops obtained with the system of Grishman and associates[5] (Fig. 2, *A*) and the authors' system* (Fig. 2, *B*) which previously was found to give good ECG correlation were normal, but those obtained with the tetrahedral system of Wilson and associates[6] (Fig. 2, *C*) indicated right ventricular hypertrophy. Right heart catheterization revealed normal pressures and an absence of shunts.

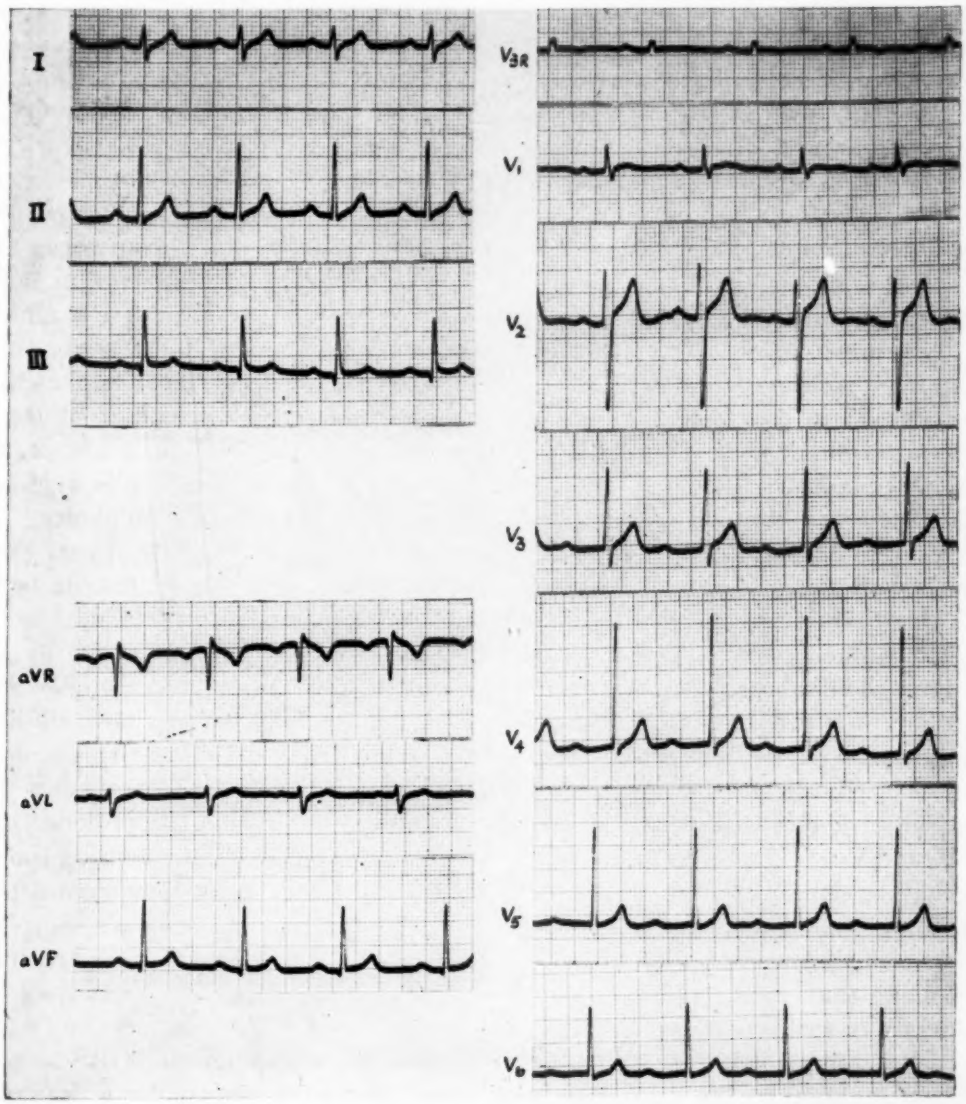


Fig. 1.—Routine ECG. Note R/S ratios in V_3R and V_1 and absence of any "mirror" relationship between V_3R and V_6. The only other abnormality is the varying and prolonged P-R interval.

*X lead is Lead I; Y lead is forehead vs. left leg; Z lead is anterior midline vs. posterior midline at level of the fifth chondrosternal junctions (X-gain = Y-gain = ½ Z-gain).

DISCUSSION

The problem that arose in this patient was whether or not right ventricular hypertrophy was present, i.e., should the right precordial leads be interpreted as abnormal. The absence of clinical and radiologic evidence did not rule out this diagnosis but the cardiac catheterization finding of normal minute-work output might reasonably be taken to preclude it.

A comparison of the electrocardiograms and vectorcardiograms offers a means of determining whether the R waves in the right precordial leads are to be considered artifact. When the chest leads are correlated with the vectorcardiograms of Fig. 2, *A* and *B*, good correlation is obtained for the large amplitude deflections, $V_{2\text{-}6}$. This is particularly true for the transverse QRS loop in Fig. 2, *B*. From Fig. 2, *A* and *B* we should expect an Rs in V_6, mirrored by a Qr or QS in V_3R. A mirror pattern is to be expected, according to current VCG theory[7,8,9] because the positions of V_3R and V_6 are on roughly opposite sides of the heart, so that when the resultant heart vector points towards one it points away from the other. Subtracting V_3R from V_6 gives the bipolar tracing from these two positions: such a tracing will indicate the true direction of the resultant heart vector. Since the deflection in V_6 is much greater than in V_3R and is almost entirely positive, the vector must be directed towards V_6 and, therefore, away from V_3R, so that the main deflection in V_3R should be negative. The fact that the complex in V_3R is positive indicates an error: this must be due to Wilson's central terminal, which, by going more negative than the V_3R electrode, makes the latter appear positive. This might well be the case since there is evidence that "error" in Wilson's central terminal may be as great as 0.8 millivolts.[4] In the present case the error is such as to make the exploring electrode appear positive in V_3R, i.e., the central terminal is itself negative with respect to true zero.*

Another interesting and curious feature of this case is that the transverse VCG obtained with Wilson's system (Fig. 2,*C*) indicates right ventricular hypertrophy. The same type of argument that showed V_3R to be in error applies also to Wilson's transverse loop. When the degree of VCG-ECG correlation is studied, we see that in the precordial electrocardiograms, while the polarity of small deflections (such as those in V_3R) could be reversed by non-neutrality of the central terminal reference, this could hardly apply to the much larger deflections in V_5 and V_6. Therefore, when looking for correlation, particular attention should be paid to signals of large amplitude. We find that there is poor agreement between Wilson's transverse loop and the electrocardiograms from Leads $V_{2\text{-}6}$, but those obtained with the other two systems agree quite well with these tracings. It follows that, in this instance, the transverse loop of Wilson's system does not correctly describe the heart vectors in this plane.

It is tempting to attribute the anterior displacement of the QRS loop in Wilson's system to the central terminal error that gave rise to the R waves in the right precordial leads. This cannot be correct, however, since such displacement of the loop indicates that the back electrode was negative with respect to the central terminal, whereas the central terminal error required to make V_3R positive would reduce negative deflection in a unipolar lead and, in this

*True zero here is that which is implied when unipolar leads are derived graphically from the VCG.

case, displace the loop more posteriorly. Lateral chest films showed that the straightening of the thoracic spine which had been noted on physical examination had altered the relation of the heart to the usual landmarks used for placement of the back electrode. The level of T_7 (the level of the back electrode in Wilson's system) was considerably above that of the heart center—rendering the sagittal lead sensitive to longitudinal components of the heart vector. Lowering the back electrode to the V_9 position put it more nearly in the transverse plane of the heart, and gave a normal transverse loop.

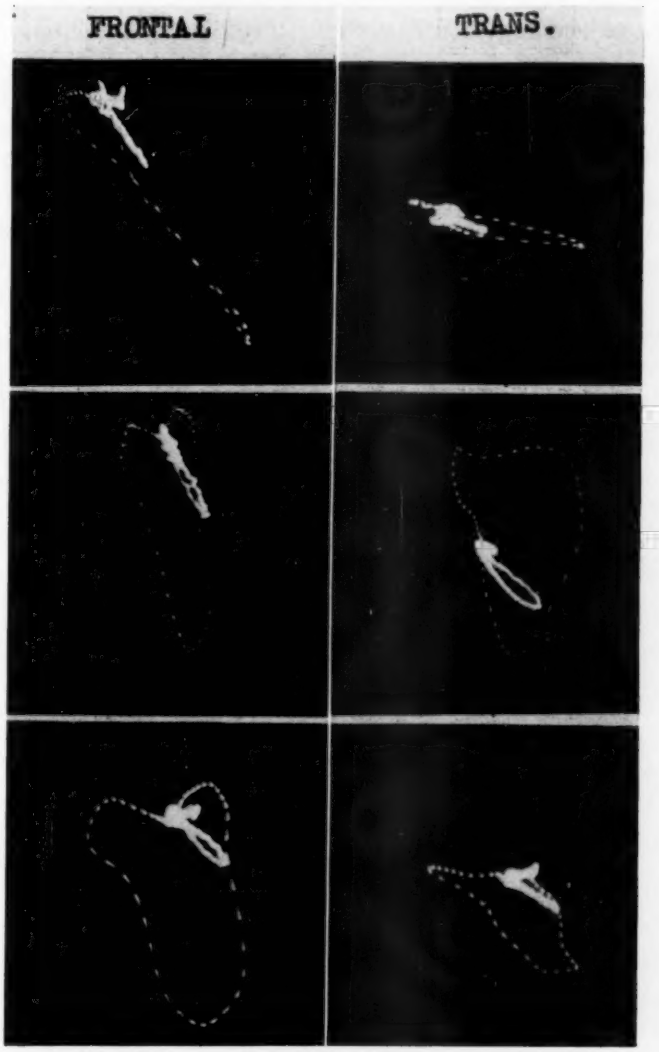


Fig. 2.—Vectorcardiograms obtained with three lead systems (sagittal views omitted). The orientation is that recommended by the American Heart Association. *A*, Vectorcardiograms obtained with the lead system of Grishman and associates. The loops are normal and correlate well with the electrocardiograms except for V_3R and V_1. *B*, Vectorcardiograms obtained with the authors' lead system (see text). The loops are normal and very good correlation is obtained with the electrocardiograms except for V_3R and V_1. *C*, Vectorcardiograms obtained with the tetrahedral lead system of Wilson and associates. The transverse loop indicates right ventricular hypertrophy but does not correlate with the large amplitude tracings of $V_{2\text{-}6}$.

SUMMARY AND CONCLUSION

A young soldier with a recent history of acute rheumatic fever had right precordial leads indicating right ventricular hypertrophy. Cardiac catheterization ruled out such a diagnosis; vectorcardiograms were taken with three different lead systems, two of which were normal, while the third again indicated right ventricular hypertrophy. This discrepancy was clarified by ECG-VCG comparison.

The ECG findings are explained on the basis of Wilson's central terminal error. The abnormal VCG is explained by a physical abnormality resulting in undue sensitivity of the sagittal lead to longitudinal components of the heart vector.

REFERENCES

1. Friedberg, C. K.: Diseases of the Heart, Philadelphia, 1956, W. B. Saunders Company.
2. Myers, G. B., Klein, H. A., and Stofer, B. E.: AM. HEART J. **35**:1, 1948.
3. Camerini, F., Goodwin, J. F., and Zoob, M.: Brit. Heart J. **18**:13, 1956.
4. Frank, E., Kay, C. F., Seiden, G. E., and Keisman, R. A.: Circulation **12**:406, 1955.
5. Grishman, A., and Scherlis, L.: Spatial Vectorcardiography, Philadelphia, 1952, W. B. Saunders Company
6. Wilson, F. N., Johnston, F. D., and Kossmann, C. E.: AM. HEART J. **33**:594, 1947.
7. Frank, E.: Circulation Res. **2**:258, 1954.
8. Duchosal, P. W., and Sulzer, R.: La Vectocardiographie, Basel, 1949, S. Karger.
9. Schmitt, O. H., and Simonson, E.: A.M.A. Arch. Int. Med. **96**:574, 1955.

INDICATIONS AND CONTRAINDICATIONS FOR OPEN CARDIAC SURGERY

HENRY A. ZIMMERMAN, M.D.,* EARLE B. KAY, M.D.,** JOHN MACKRELL, M.D.,*** AND M.P. SAMBHI, M.D.****

CLEVELAND, OHIO

THE early blind intracardiac surgical methods led to the realization that they were inadequate and that the best results were to be obtained with direct visual techniques. Initial attempts to achieve direct visualization employed either a circulatory by-pass or the use of hypothermia to permit the surgeon a brief period to accomplish this. The introduction of a pump and oxygenator has revolutionized the intracardiac approach by safely allowing adequate time for both exploration and corrective surgical procedures. In the past 15 months we have been using a rotating disc-type oxygenator with a Sigmamotor pump in our institution. A total of 72 cases have been operated upon with open cardiotomies.

Since the mechanics of the above by-pass has been well confined within the limits of safety, further progress in this surgical approach depends upon improvement in operative techniques and experience in selecting the patients. The technical improvement in direct vision cardiac surgery is moving at a rapid pace, but the experience in the selection of patients, by necessity, lags behind. The indications and contraindications for open heart surgery at this time are not crystallized, so that our comments may be considered as a glimpse of a rapidly moving object. The principal emphasis in approach to the patient with congenital heart disease today is in the direction of corrective rather than palliative procedures.

In the cases of congenital heart disease that we have operated upon here, we have found that multiplicity of defects were not uncommon. We have arbitrarily classified our discussion into isolated and combined lesions for the purpose of simplicity. We are disregarding an intricate discussion of the complex lesions and placing the main emphasis on the isolated defects.

ISOLATED VENTRICULAR SEPTAL DEFECTS

In the cases undergoing physiologic studies and cardiac evaluation, 20 cases were considered to have isolated interventricular septal defects. One fifth of these cases, having been referred to us because of a murmur with absence of

Received for publication June 25, 1957.

*Chief of Cardiovascular Service and Director of the Marie L. Coakley Cardiovascular Laboratory, St. Vincent's Charity Hospital, Cleveland, Ohio.

**Chief of Thoracic and Cardiovascular Surgical Service, St. Vincent's Charity Hospital, Cleveland, Ohio.

***Chief of Pathology, St. Vincent's Charity Hospital, Cleveland, Ohio.

****Marie L. Coakley Cardiovascular Fellow, St. Vincent's Charity Hospital, Cleveland, Ohio.

TABLE I. INTERVENTRICULAR SEPTAL DEFECTS

NAME	AGE (YEARS)	OXYGEN CONTENT (IN VOL. %)						PER CENT SATURATION	PRESSURES (IN MM. Hg)				OPERATIVE RESULTS
		SVC	IVC	RA	RV	PA	FA or BA		RA	RV	PA	FA or BA	
B.S.	7	9.9	8.5	9.8	12.2	11.9	13.6	94.9	5/2	36/3	40/7	148/80	Good
Y.J.	5	8.8	10.6	9.9	12.1	11.6	14.2	98.2	9/3	37/5	34/13	100/56	Good
R.J.	8	10.1	10.1	10.3	12.2	11.9	13.9	93.4	9/4	42/1	27/12	109/60	Good
S.P.	9	10.8	10.6	11.2	14.4	13.8	14.6	93.4	19/11	68/2	68/24	128/64	Good
P.R.	2	6.3	7.4	6.8	8.6	8.8	9.7	92.4	6/1	54/4	56/20	88/44	Good
R.P.	2½		8.4	8.0	10.2	9.3			8/5	80/12	88/44	108/88	Fair
M.B.	4	7.7	8.8	8.3	12.0	11.1	12.3	93.9	10/7	80/8	80/26	108/68	Poor
R.S.	5	8.3		9.5	11.8	11.5			5/2	45/0	42/10	78/57	Good
J.M.	25	13.1	13.3	13.9	15.9	16.3	18.1	93.9	8/3	70/3	72/35	108/62	Good
L.D.	10	8.9		8.0	11.8	12.0	13.9	95.9	7/3	85/7	75/32	110/56	Died (Incidental)
L.J.	4½	6.3		5.6	7.8			86.3	12/8	80/4		108/78	Good
K.D.	4	12.6	12.5	14.6	15.1		15.1	90.5	5/1	88/6		88/44	Died
D.J.	5	13.6	14.1	13.6	15.3	16.7			13/4	110/0	108/50	106/60	Died
S.G.	12	9.3	9.1	8.9	11.9	13.3	13.3	90.9	7/2	76/4	80/40	80/50	Died
R.A.	2½	6.5	9.3	7.4	12.2	11.4			5/2	80/6	86/40	80/40	Died
F.J.	4	9.6	8.4	8.7	10.5	12.5	14.2	95.1	8/0	90/0	75/40	?	Died

SVC—superior vena cava; IVC—inferior vena cava; RA—right atrium; RV—right ventricle; PA—pulmonary artery; FA or BA—femoral or brachial artery.

symptoms, was not recommended to have surgical correction because of the absence of cardiac enlargement, normal electrocardiograms, pressure in the right ventricle averaging 30 mm. Hg, and an increase of no more than 1.0 volume per cent in oxygen content of a blood sample from the right ventricle as compared with the right atrium. An interventricular septal defect of this nature, by virtue of its small size, prevents any sizable shunt to cause any significant increase in the pulmonary blood flow. These are cases of so-called *maladie de Roger* which have been considered benign. They may remain stable, but we recommend that they be re-evaluated after 2 or 3 years to make certain that they are not progressive.

Direct visual repair of the interventricular septal defect was carried out in the remaining 16 cases. In these, the septal defects were large enough to cause a significant increase in the pulmonary blood flow. The brunt of the larger flow is borne by both the right ventricle and the pulmonary arteries, with the consequent development of right ventricular hypertrophy and pulmonary hypertension. Hence, in the evaluation of a ventricular septal defect we need to assess all of the above factors.

A. *Pressure Determinations.*—In Table I are presented the physiologic studies and the operative results in these 16 cases. It is apparent from the data in the table that all those cases who failed to survive had pressures in their pulmonary arteries around 80 mm. Hg, or higher. Those who survived with such high pressures did not achieve a good result. On the other hand, all the cases with pressures well below 80 mm. Hg in their pulmonary arteries did well postoperatively. A closer analysis of these cases brings out further important considerations.

In Table II we have singled out 8 cases having pressures in their pulmonary arteries equal to or greater than 80 mm. Hg. Four of these cases survived the operation. It should be noted that in those cases who survived, the pulmonary artery pressure had not exceeded 75 to 80 per cent of their systemic arterial pressure. Furthermore, the diastolic pressures in the pulmonary artery were lower in comparison to the fatal cases. On the other hand, the cases who died had almost equal pressures in the pulmonary and systemic arteries.

TABLE II. ANALYSIS OF CASES OF VENTRICULAR SEPTAL DEFECT WITH HIGH PRESSURE IN THE RIGHT SIDE OF THE HEART

SURVIVALS / FATALITIES	SYSTOLIC RV	SYSTOLIC PA	DIASTOLIC PA	BA or FA	% RATIO PA/BA
S	80	88	44	108	81%
S	80	80	26	108	74%
S	85	75	32	110	68%
S	80	x	x	108	74%
F	88	x	x	88	100%
F	110	108	50	106	100%
F	76	80	40	80	100%
F	80	86	40	80	100%

Important hemodynamic deductions can be made from the above. Both the pressure determinations as well as measurements of pulmonary blood flow are required to give an idea about the magnitude of the total resistance in the pulmonary vascular tree. However, the level of the pressures alone does give some information about the other two factors. For instance, the diastolic pulmonary arterial pressure provides a workable index of pulmonary resistance.

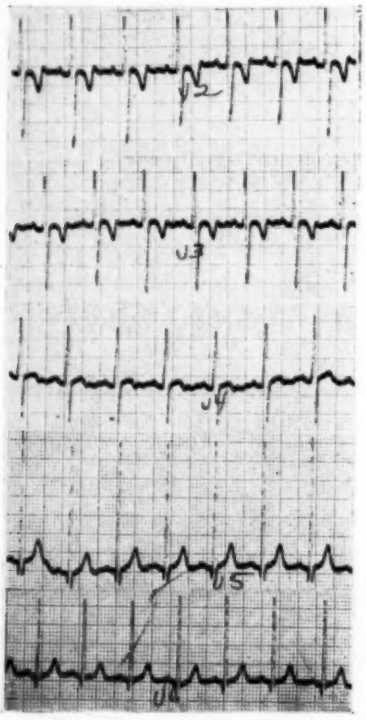


Fig. 1.

Furthermore, as pulmonary and systemic pressure levels approach one another, a concomitant decrease in the left-to-right shunt can be postulated. Conversely, a wide differential of pressure levels in the greater and lesser circulation assures the presence of a sizable intracardiac shunt.

In our fatal cases, death occured usually in the immediate postoperative period. These children developed low systemic arterial pressures and succumbed in a apparent state of pulmonary edema. The weight of evidence, including our own observation, does not support the argument that right ventricular failure is responsible for the above picture. In our opinion, it is the left ventricle which becomes unable to compensate for the altered burden thrust upon it by the sudden change in hemodynamics. DuShane and associates[1] achieved good results after repair of interventricular septal defects in their cases having a dominant left-to-right intracardiac shunt. This held true irrespective of a high magnitude of pulmonary arterial resistance and the presence of a reversed shunt. Our own experience leads us to concur with these investigators. Thus, in those cases in which the left ventricle had been accustomed to a large left-to-right shunt, a change in the direction of equalization of pressures in the pulmonary and sys-

temic circuits, concomitant diminution of left-to-right shunt, and a probable increase of reversed shunt when acting over an extended period of time alters the functional capacity of the left ventricle in such fashion that it fails when expected to assume the full burden of the systemic circulation after closure of the interventricular septal defect. At present, the thinking in this direction is one of conjecture. The pathologic findings in these cases have revealed some dilatation of the left ventricle.

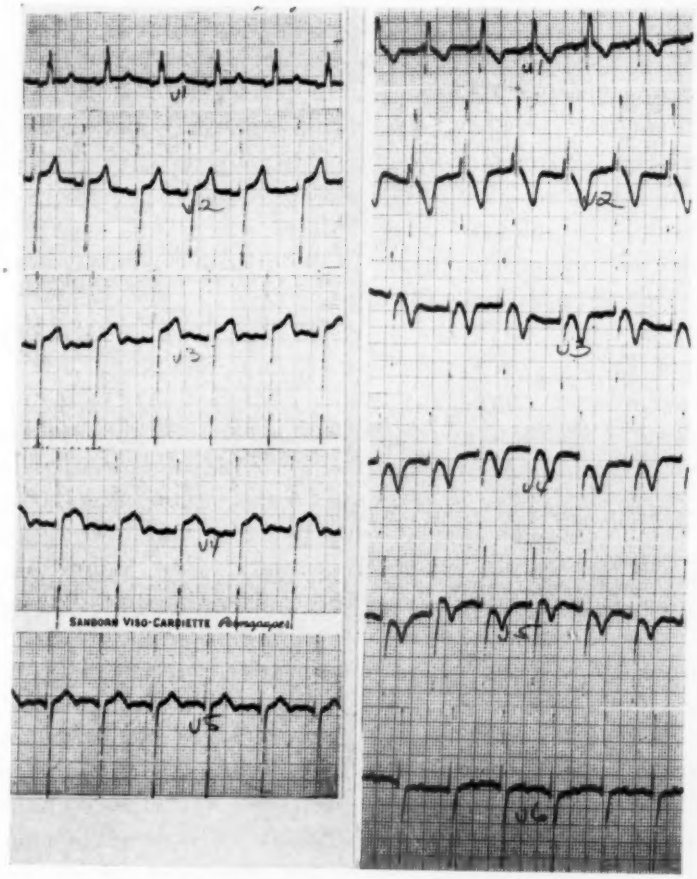


Fig. 2.

B. *Shunt Flow Estimations.*—Calculation of shunt flow by the Fick principle is technically difficult in infants and small children, because of the difficulty of determining the oxygen consumption. However, in cases of dominant left-to-right shunt, the percentage of shunt flow can be calculated from the ratio of pulmonary and systemic arteriovenous difference. On the other hand, it is well known that, in cases with right and left intraventricular pressures approaching one another and the presence of bidirectional shunts, the intermingling of blood displaces the use of oxygen content values for these calculations. Moreover, oxygen content of arterial blood becomes an unreliable index of a right-to-left shunt when it is affected by the presence of incipient congestive cardiac failure, diffusion defects

in the pulmonary capillaries, and defective aeration of the lungs in cases done under anesthesia. However, it is reported that dependable shunt flow determinations can be made by employing dye dilution curve techniques in the above situations.

In our experience, a careful interpretation of the electrocardiogram, employing the criteria of Cabrera and Monroy[2] for the systolic and diastolic overloading of the heart, has been of sufficient value in most cases to permit a prediction of the dominant shunt. In the presence of a dominant left-to-right shunt, the left ventricle shows the pattern of diastolic overloading (Fig. 1).

Notice the peaked upright T waves and high R waves in the left-sided precordial Leads V_5 and V_6 and deep S wave in V_2 and V_3. As the pulmonary resistance rises and the left-to-right shunt diminishes, the diastolic overload pattern of the left ventricle disappears and the T waves in the left-sided leads start flattening. This flattening of T waves was consistently present in our cases with equalizing pressures in pulmonary and systemic arteries. From the appearance of a systolic overloading pattern of the right ventricle we have further surmised that a right-to-left shunt is probably present (Fig. 2).

These are the electrocardiograms of the same case 9 months apart. Notice the flattening of T waves in V_5 and V_6 and a more deeply inverted T wave with a higher R wave in V_1 in the later graph.

C. *Pulmonary Vasculature.*—A crucial problem in the management of cases of interventricular septal defects has been the development of increased pulmonary vascular resistance as a response to the greatly augmented pulmonary blood flow. This increased vascular resistance acts as a limiting factor upon the volume of blood that can flow through the lungs. The magnitude of this resistance, in relation to the systemic resistance, determines the dominance of shunt flow.

During fetal life the small intrinsic muscular pulmonary arteries in a range from 40 micra to less than a millimeter in diameter have a thicker media than is seen in other vessels. It has been assumed because of this muscular hypertrophy that these vessels act as a part of the regulatory mechanism in the fetal vascular shunts. A portion of the blood returning to the right atrium is channeled through the foramen ovale into the systemic circulation. The remainder passing into the pulmonary arterial system is partly diverted through the ductus arteriosus into the aorta. Many consider that the constriction of these small pulmonary arteries produces a physiologic increase of pulmonary vascular resistance in the fetus and thus serves adequately in the diversion of blood flow from these vessels. The mechanism effecting such changes may be either neurogenic or humoral in nature, or due to the unexpanded state of the lungs. After birth, with the establishment of respirations and the normal dual circulation, the cardiac shunts rapidly cease to function. In the normal infant these small arteries have a prominent media which becomes progressively less during the first few months of life.

In cases with interventricular septal defects the small muscular pulmonary arteries may respond to the increased pulmonary blood flow by developing a significant increase in the thickness of their walls. A considerable variation ranging from absence to different degrees of severity may be seen, dependent

upon the size of the defect, duration of the disease, and other unrecognized hemodynamic factors. The cases showing change may range from mild to severe. The principal changes in these small muscular arteries are medial hypertrophy, intimal thickness due to fibroelastic proliferation, hyaline deposits and thickened endothelium, and thickening, splitting and hyperplasia of the elastic lamina. These changes produce varying degrees of narrowing of the vascular lumens. Angiomatous transformation has not been demonstrated in our cases of interventricular septal defects. Paradoxically, the changes are neither uniform nor

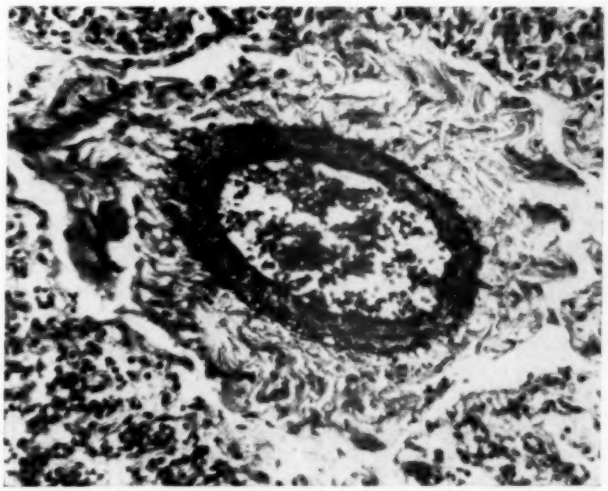


Fig. 3.—Normal pulmonary artery. Female aged 3 years. Verhoeff's elastic-Van Gieson stain x 265. (Reduced ¼.) Note internal elastic lamella bordering lumen with endothelial lining and lack of intimal cushion.

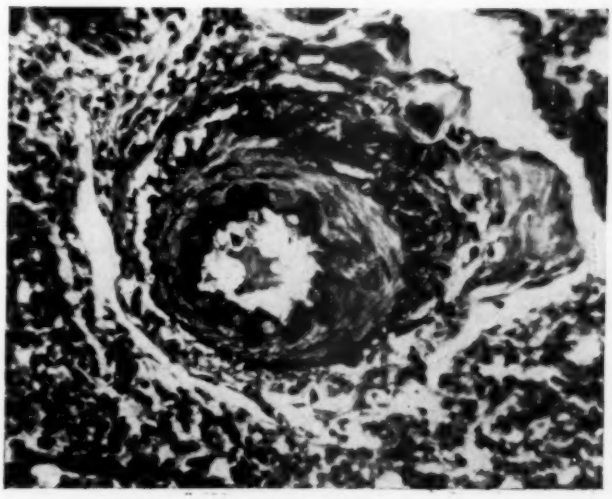


Fig. 4.—Moderate arterial disease. Female aged 18 months. Verhoeff's elastic-Van Gieson stain x 300. (Reduced ¼.) Prominent medial hypertrophy, lack of intimal widening. Same reduction of lumen.

diffuse. Although grading the extent of the lesions can be misleading, we have found it helpful to classify our cases as either negative or slight, moderate or markedly involved. The numerical involvement per microscopic field has been a more valuable criterion than the degree of change seen in a given vessel. The photomicrographs (Figs. 3-8) illustrate the changes that we have observed in some of our cases.

It is of interest to point out that in cases with either pulmonic or subpulmonic stenosis we have found the pulmonary arteries of the various sizes to have

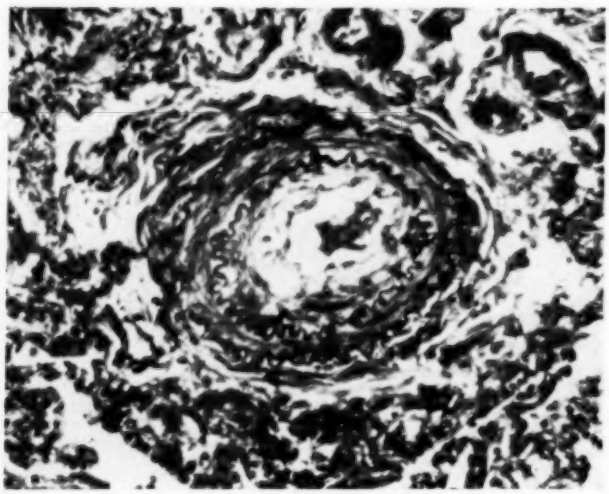


Fig. 5.—Moderate arterial disease. Male aged 5 years. Verhoeff's elastic-Van Gieson stain. (Reduced ¼.) Moderate degree of intimal widening, more fibrillar than cellular. Prominent elastic lamella. Moderate reduction of lumen.

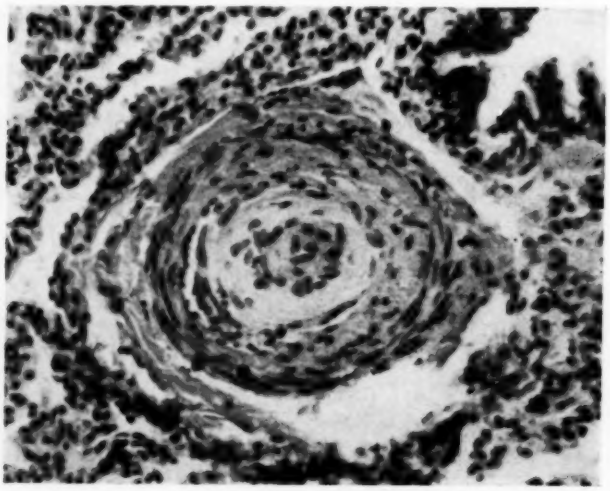


Fig. 6.—Marked arterial disease. Male aged 18 months. Hematoxylin-eosin stain x 300. (Reduced ¼.) Marked intimal cellular proliferation, hyaline material in intima, tiny lumen.

thin walls, often of less prominence than would be expected normally. It may thus lead to the inference that the arterial changes are a consequence of the increased pulmonary flow and pressure load.

There is much to be desired in the preoperative clinical evaluation of these vessels. We have attempted with partial success to predict something about the state of these vessels by noting the response of pulmonary arterial pressure to (1) inhalation of 100 per cent oxygen, (2) intracatheter aminophylline, and (3) exercise.

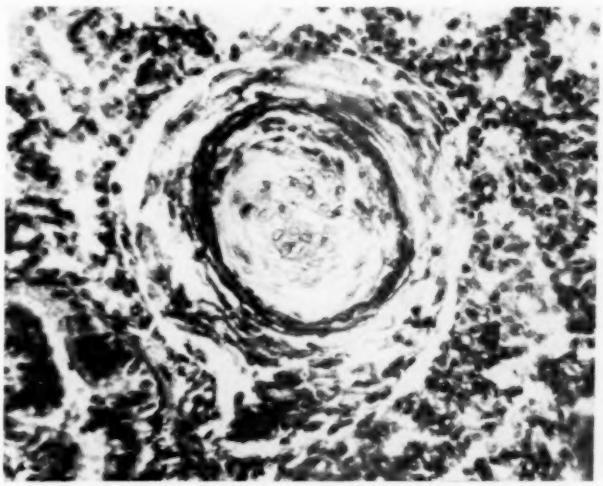


Fig. 7.—Marked arterial disease. Female aged 5 years. Verhoeff's elastic-Van Gieson stain x 300. (Reduced ¼.) Marked intimal proliferation. Prominent elastic lamellae, inconspicuous media, small lumen.

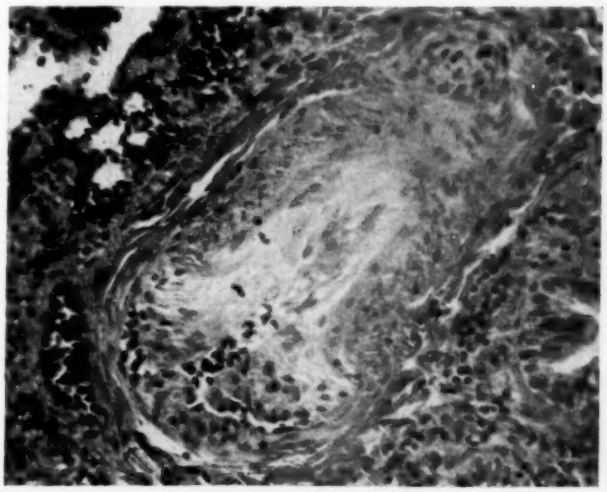


Fig. 8.—Marked arterial disease. Male aged 18 months. Hematoxylin-eosin stain x 300. (Reduced ¼.) Intimal cellular proliferation. Mitotic activity. Marked reduction in size of lumen.

TABLE III. CATHETERIZATION DATA IN PATIENTS WITH ISOLATED INTERATRIAL SEPTAL DEFECTS

PATIENT	AGE (YEARS)	O_2 SATURATION OF BLOOD				% SHUNT FLOW	RV PRESSURE (MM. Hg)	PA	RESULT
		SVC-IVC / 2	RA	PA	BA or FA	PULMONARY A-V DIFFERENCE VS. SYSTEMIC A-V DIFFERENCE			
R.T.	13	11.5	13.3	13.6	14.6	67%	35/6	23/8	Excellent
D.C.	6	8.8	12.6	13.5	14.5	82.5%	40/0	19/7	Excellent
J.G.	5	9.3	13.6	12.1	13.3	79%	40/3	27/12	Died
J.B.	15	17.0	20.0	19.5	20.5	71%	42/0	40/5	Excellent
K.M.	42	11.3	14.1	14.0	15.2	53%	55/10	x	Excellent
L.R.	6	12.7	15.5	15.7	16.4	61%	42/0	40/18	Excellent
R.M.	12	13.3	15.3	15.3	16.4	65%	27/–2	17/7	Excellent

The magnitude of the rise in systolic and diastolic pressure in the pulmonary artery following exercise and the time taken by it to return to normal levels may roughly quantitate the loss of pulmonary reserve to accommodate an increase in flow. A drop of 10 to 15 mm., or a 20 per cent drop, of mercury in the diastolic pressure of the pulmonary artery or its failure to do so within 5 minutes of inhalation of 100 per cent oxygen or injection of aminophylline into the catheter has led us to postulate a tentative classification of the pulmonary vascular bed as being either "responsive" or "nonresponsive." The exact implication of this classification remains to be clarified. The effect of ganglionic blocking agents in these patients with a view to discovering any element of neurogenic control of these vessels is under investigation.

The electrocardiogram again has been of some help in this evaluation. In the early stages of ventricular septal defect, about 60 per cent of the cases showed the pattern of diastolic overloading of the right ventricle. In cases who had developed markedly elevated pressures in the pulmonary circuit, and consistently so in our fatal cases with pulmonary resistance approaching the systemic levels, a superimposition of the pattern of systolic overloading of the right ventricle was noted, thus giving the pattern of so-called "composite overloading pattern" (refer to Fig. 2). It is of interest to compare this with the electrocardiographic changes in isolated pulmonic stenosis where a pure pattern of systolic overloading is seen.

In our last 8 cases of open heart surgery we undertook an evaluation of pulmonary vasculature employing frozen sections of lung biopsies taken after thoracotomy, before the cardiac portion of the operation had been started. These sections were stained with hematoxylin and eosin. The degree of arterial disease was classified on the basis of the previously described criteria. We found that the prediction of the degree of vascular change by physiologic and electrocardiographic findings were supported histologically. In those cases who were interpreted as having advanced changes in the pulmonary vessels, our surgeons considered a Blalock type of shunt, either alone or in conjunction with closure of the septal defect.

In summary then, to our knowledge at present, the ideal time for repair of a ventricular septal defect is when pulmonary artery pressures are below 75 per cent of the systemic arterial pressure. At this time these cases have a large left-to-right shunt, the evidence for which can usually be picked up in the electrocardiogram as a diastolic overload pattern of the left ventricle. A significant drop of pulmonary artery pressure after aminophylline and 100 per cent oxygen speaks in favor of a good postoperative result. The superimposition of a systolic overloading pattern of the right ventricle associated with flattening of T waves in the left-sided leads mitigates the chances of a good result.

INTERATRIAL SEPTAL DEFECTS

Cardiac catheterization data with operative results are presented in 7 cases on whom the pump oxygenator was used for repair of interatrial septal defect as a single lesion (Table III). There was 1 death among these cases. The age range of this group was from 5 to 42 years.

In each of these cases there was a difference of more than 2 volumes per cent in the oxygen content of mixed venous blood and right auricular sample. According to Kjellberg and associates,[4] the shunt flow in the interatrial septal defects is spread, but throughout the cardiac cycle. Possibly the major portion of it occurs in the ventricular diastole as suggested by Dexter.[5] The suction effect of the diastolic stretch of the comparatively thin-walled right ventricle may be one explanation for it.[5] In contrast, the main shunt flow in cases of interventricular septal defects should occur during ventricular systole. It is of interest to note that with comparative amount of shunt flows in these two differently located septal defects the increased pulmonary resistance develops much later in cases of interatrial septal defect. The reason why this flow which is spread out in atrial septal defects is better tolerated by pulmonary vessels is not clear, but it gives rise to some interesting conjectures as to the occurrence of the shunt flow in different phases of the cardiac cycle possibly having something to do with it.

All 7 of our cases were symptomatic. Symptoms probably occurred on the basis of the low output from the left ventricle. The increased pulmonary flow was evident as prominent lung markings on the roentgenogram in all cases. The dilatation (diastolic stretch) of the right ventricle gave rise to enlargement of the radiographic cardiac shadow and a pattern of diastolic overloading of the right ventricle in the electrocardiogram.

In our series there were no patients who had reversed shunts and cyanosis. Apart from those, we recommend that all interatrial septal defects be repaired, except the asymptomatic cases with insignificant shunt flow showing no roentgenographic or electrocardiographic abnormalities.

PULMONIC STENOSIS

Eight cases of simple valvular pulmonic stenosis (Table IV) were operated upon by open cardiotomies. There were no mortality among these.

The gradient across the pulmonic valve in these cases varied from 29 to 142 mm. Hg. Roentgenologic enlargement of the cardiac shadow was seen in only 1 of these cases, and this case had the highest pressure in the right ventricle in the series. In the rest of the cases the cardiac size was interpreted as being within normal limits. This is consistent with the concept of concentric hypertrophy without dilatation. Decrease of lung markings was always a questionable finding. In some of the cases, the postoperative dilatation of the pulmonary artery gave an impression of prominent outflow tract of the right ventricle and unequal hilar shadows on the two sides.

Electrocardiograms displayed a pure pattern of systolic overloading of the right ventricle in all but 2 cases.

Notice the high R wave and deep inverted T wave in Lead V_1 in Fig. 9.

Right ventricular pressure of 75 to 100 mm. Hg has been recommended as an indication for operation by Brock[7] and others. We have learned not to rely on right ventricular pressure alone; furthermore the height of this pressure has not been a contraindication in our experience.

In the presence of a definite diagnosis with a systolic gradient of 20 or more mm. Hg across the pulmonic valve, we would recommend the operation even if the child is asymptomatic, especially so in the presence of electrocardiographic signs. As already mentioned, the hypertrophy of the right ventricle will not produce enlargement of the radiographic cardiac shadow until very late stages.

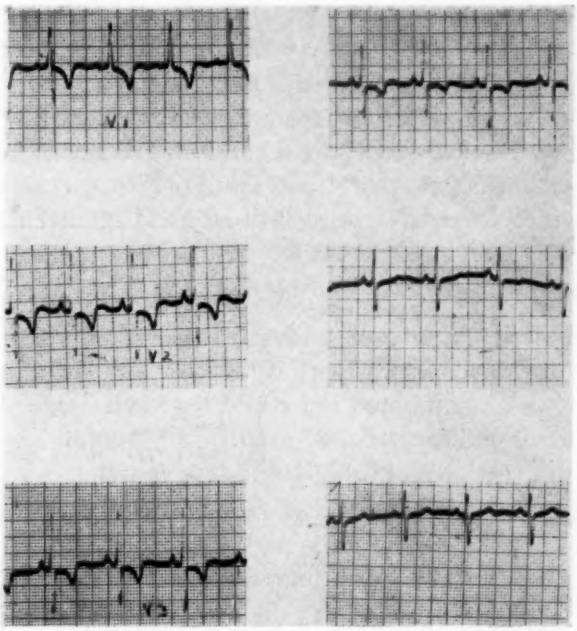


Fig. 9.

TABLE IV. SIMPLE PULMONIC STENOSIS

PATIENT	AGE (YEARS)	PRESSURE IN RV	PRESSURE IN PA	SYSTOLIC GRADIENT	SYSTOLIC LOAD IN ECG	SYMPTOMS
P.T.	8	160/4	18/13	142	Marked	Marked
O.R.	9	85/0	10/0	75	None	None except failure to grow
G.J.	3	96/4	18/10	78	Moderate	Minimal
K.E.	4	48/0	15/6	33	Moderate	Moderate upper respiratory infection
H.L.	3	44/6	15/9	29	Diastolic Loading	None
B.S.	9	80/0	19/11	61	Marked	Marked
N.A.	28	150/10	18/10	132	Marked	Marked
G.K.	3	88/0	15/8	74	Moderate	None

As regards the time of operation, certainly in an asymptomatic infant with this diagnosis it would be wise to wait with the operation until the age of 4 to 6 years, at which time the child becomes a much better technical risk. On the other hand, the dangers of waiting too long should be kept in mind. Brock,[7] 1952, pointed out that, although the congenital pulmonic stenosis may not be progressive itself, yet its failure to grow in comparison with the rest of the body gives rise to progressive disability, especially so in the rapid growth period of adolescence.

The normal growth of the child with this congenital lesion may be adversely affected on account of a low output from the left ventricle. Moreover, Gibson[8] has stressed that, in his experience, these children are apt to take a rather abrupt turn in the course of their disease from an apparently compensated state to a poor condition, which increases the risk of surgical intervention many fold.

COMBINED LESIONS

Relatively limited experience and more uncertain prognosis in regard to combined lesions does not permit us to crystallize any specific indications. However, since patients with combined lesions do not do well when left to themselves and succumb to their malformations, usually at a young age, we feel that this fact justifies the undertaking of a higher operative risk.

It is premature at this time to comment on the indications for lesions like transpositions of great vessels or atrioventricular communis. In this discussion we will comment only briefly on patent ductus arteriosus with additional malformations and tetralogy of Fallot.

Corrective surgery was performed on 2 cases of patent ductus arteriosus with additional malformations in our institution. One of these cases with associated pulmonic stenosis had a good result from surgery. The other patient had associated interventricular septal defect and patent foramen ovale. This patient had equal levels of pressure in the right ventricle and ascending aorta, with arterial blood oxygen content of 81 per cent; he died following surgery. The poor outlook in such patients following corrective surgery has been reported by Ellis and associates.[9] Hence, to our knowledge at present, radical surgery may not be indicated in these subjects.

Direct visual repair was carried out in 9 patients with a diagnosis of tetralogy of Fallot. As is exemplified by the 2 aforementioned cases of patent ductus arteriosus, the association of pulmonic stenosis with the congenital defects allowing a left-to-right shunt acts as a protective mechanism against the development of of pulmonary arteriosclerosis. In these cases of tetralogy of Fallot, it was the severity and the site of the pulmonic stenosis that seemed to decide a favorable or unfavorable postoperative outcome. Infundibular pulmonic stenosis, being technically a more difficult problem, carries a greater risk with it, otherwise the the size of the ventricular septal defect or presence or absence of apparent overriding of the aorta did not seem to affect the ultimate outcome.

The best results were achieved in cases with low-grade pulmonic stenosis. In cases with stenosis of extreme degree, hypoplasia and subnormal recorded

pressures in pulmonary artery (around 10 to 20 mm. Hg), death resulted in the postoperative period. To achieve a good result the pulmonary bed must be adequately developed to take the increased blood flow following opening of the pulmonic valve.

SUMMARY

Present-day criteria for selection of patients for open heart surgery are discussed on the basis of experience gained on 65 patients. The development of pulmonary arteriosclerosis in cases of malformation with a left-to right shunt is the major factor in the circumstances that mitigate good postoperative results. With the advent of open heart surgery for congenital heart disease, the emphasis has come to be placed on corrective rather than palliative procedures.

REFERENCES

1. DuShane, J. W., et al.: J.A.M.A. **160**:950, 1956.
2. Cabrera C., E., and Monroy, J. R.: AM. HEART J. **43**:661, 1952.
3. Zimmerman, H. A.: Dis. Chest **20**:46, 1951.
4. Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B.: Diagnosis of Congenital Heart Disease, Chicago, 1955, The Year Book Publishers, Inc.
5. Dexter, L.: Brit. Heart J. **18**:209, 1956.
6. Brecher, G. A.: Personal communication.
7. Brock, R. C.: Am. J. Med. **12**:706, 1952.
8. Gibson, S., et al.: A.M.A. Am. J. Dis. Child. **87**:27, 1954.
9. Ellis, F. H., Jr., et al.: J. Thoracic Surg. **31**:268, 1956.
10. Dexter, L.: Surgery in Heart Disease, (Disease-a-Month Series), Chicago, 1956, The Year Book Publishers, Inc.

COMBINED QUINIDINE AND PROCAINE AMIDE TREATMENT OF CHRONIC ATRIAL FIBRILLATION

MERVIN J. GOLDMAN, M.D.

OAKLAND, CALIF.

WITH the judicious use of quinidine, successful conversion of chronic atrial fibrillation can be accomplished in over 80 per cent of cases. The incidence of conversion is higher (± 87 per cent) in the group with degenerative heart disease (coronary arteriosclerosis and hypertension) and lower (± 55 per cent) in the rheumatic group with mitral valvulitis.[1,2,3]

Procaine amide alone has been relatively successful in conversion of paroxysmal atrial fibrillation, but the value of this drug in the conversion of chronic atrial fibrillation has been inferior to that of quinidine.[4]

The patient with chronic atrial fibrillation, even though well compensated, is still prone to embolic phenomena. Furthermore, such a patient in chronic heart failure may be greatly benefited by conversion to sinus rhythm.

In an attempt to increase the incidence of conversion, the combined effect of quinidine plus procaine amide has been investigated.

METHOD

The patients selected were those who could not be converted on quinidine alone. The maximum dose of quinidine given per day ranged from 4 to 6 Gm. (1 Gm. every 6 hours or 1.2 Gm. every 2 hours for 5 doses). When unsuccessful, quinidine was discontinued for at least 4 days. In the initial 4 cases procaine amide alone was used in increasing doses to a maximum of 8 Gm. per day (1 Gm. every 3 hours). No favorable results were obtained and therefore the use of procaine amide alone was abandoned.

Combination of quinidine and procaine amide was then begun (after at least 4 days had elapsed since any previous therapy with quinidine or procaine amide individually). Beginning doses ranged from 0.2 Gm. quinidine plus 0.25 Gm. procaine amide every 6 hours, to 0.4 Gm. quinidine plus 0.5 Gm. procaine amide every 6 hours. The patients were kept on the same dose for 3 days, and at intervals of 3 days the dose of either quinidine alone or quinidine plus procaine amide was increased. The maximum dose used to date has been 1.0 Gm. quinidine plus 0.75 Gm. procaine amide every 6 hours.

The same precautions were used as when administering quinidine alone. That is, the patient was observed clinically and the pulse and blood pressure were taken prior to each dose of medication; electrocardiographic strips (Leads aV_R, aV_F and V_1) were taken at least once daily, and more often as indicated.

From the Veterans Administration Hospital, Oakland, Calif.
Received for publication June 25, 1957.

All patients received digitalis and other medications as indicated. Every effort was made to reach optimum cardiac status prior to attempted conversion. In no instance was there evidence of any active process such as active rheumatic fever or intercurrent infection which would make conversion at one time more difficult than at another time.

A total of 38 patients has been studied to date. The etiology was degenerative in 18 patients, and rheumatic with mitral stenosis or mitral stenosis and insufficiency in 20.

RESULTS

Thus, in 50 per cent of 38 cases who were not converted on quinidine therapy alone, conversion was successful with a combination of quinidine and procaine amide treatment. The disparity between the incidence of successful conversion in the degenerative versus the rheumatic group with quinidine alone is not evident in this study. This is explainable, since all patients were initially "quinidine failures."

TABLE I

	CONVERSIONS	FAILURES
Total	19	19
Degenerative	9	9
Rheumatic	10	10

TABLE II. DOSAGE*

CONVERSION DOSE		NUMBER	MAINTENANCE DOSE		NUMBER
QUINIDINE	PROCAINE AMIDE		QUINIDINE	PROCAINE AMIDE	
0.4	0.5	8	0.4	—	8
0.6	0.5	7	0.4	—	5
			0.6	—	1
			0.4	0.5	1
0.8	0.5	3	0.6	—	1
			0.4	0.5	2
1.0	0.75	1	0.6	0.5	1

*All doses are in grams every 6 hours.

It is to be emphasized that all the patients in Table II had previously received 4 to 6 Gm. of quinidine alone per day. Thus, even if procaine amide were to be considered as equally efficacious, gram for gram, as quinidine (and this is probably not true), the total daily dose of both drugs at the time of conversion in the majority of cases was less than the previous daily dose of quinidine alone. It is therefore reasonable to assume that the combination of these two medications is not merely additive but actually synergistic.

Following conversion, maintenance therapy with quinidine alone was possible in 15 of the 19 patients. Four required quinidine and procaine amide in combination for maintenance of regular sinus rhythm.

CASE ILLUSTRATIONS

W. B., aet. 41. Diagnosis: Rheumatic heart disease, inactive, with mitral stenosis, cardiac insufficiency, and chronic atrial fibrillation. The patient had suffered a recent cerebral embolus. In spite of bed rest, digitalis, sodium restriction, and diuretics, the patient remained a bedridden invalid in chronic heart failure. Conversion was attempted with quinidine up to a maximum of 6 Gm. per day for 3 successive days. Atrial fibrillation persisted. Conversion was accomplished with 0.6 Gm. quinidine plus 0.5 Gm. procaine amide every 6 hours. Following conversion the patient lost all signs of heart failure, became fully ambulant and was maintained on 0.4 Gm. quinidine plus 0.5 Gm. procaine amide 4 times daily. On this dosage he has remained in regular sinus rhythm for 4 years.

D. D., aet. 57. Diagnosis: Rheumatic heart disease, inactive, with mitral stenosis, cardiac insufficiency, and chronic atrial fibrillation. The patient had sustained one pulmonary embolus and one cerebral embolus while fibrillating. The heart failure responded well to digitalis and sodium restriction, and conversion was attempted in an effort to prevent future embolic phenomena. This was unsuccessful on a maximum daily dose of 6 Gm. of quinidine. Subsequently, conversion was successful with 0.4 Gm. quinidine plus 0.5 Gm. procaine amide 4 times daily. The patient has been maintained in regular sinus rhythm and free of further emboli for 3 years with 0.4 Gm. of quinidine 4 times daily.

TOXICITY

In no instance was it necessary to discontinue combined therapy because of a fall in blood pressure. In 3 patients, combination therapy had to be abandoned because of distressing nausea and vomiting. However, 5 patients who complained bitterly of gastrointestinal disturbances when on larger doses of quinidine alone, were successfully converted on smaller doses of quinidine, plus procaine amide, without any distress.

In 1 patient, combined therapy was discontinued because of an increase of 50 per cent in the QRS interval. In no instance were serious ventricular arrhythmias or atrioventricular nodal rhythm encountered.

No embolic phenomena were encountered at the time of conversion or subsequent to conversion. In contrast, 6 of the 19 converted cases had manifested pulmonary or systemic emboli prior to conversion.

CONCLUSIONS

This study indicates that a substantial number of patients (50 per cent in this series) with chronic atrial fibrillation can be converted to regular sinus rhythm with a combination of quinidine and procaine amide therapy, when quinidine alone has been unsuccessful. In the majority of cases, the total dosage of the 2 drugs was less than that of quinidine alone. This suggests a synergistic action of these 2 drugs rather than a simple additive effect. There has been less gastrointestinal toxicity with combination therapy than on the larger doses of quinidine alone. No serious toxicity has been observed with the combined therapy. Nonetheless, proper precautions must be observed, since improper use of these drugs could result in serious toxicity.

SUMMARY

Of 38 patients with chronic atrial fibrillation who could not be converted with quinidine alone, 50 per cent have been converted to and maintained in regular sinus rhythm with smaller doses of quinidine administered in combination with procaine amide.

REFERENCES

1. Sokolow, M.: Am. Heart J. **42**:771, 1951.
2. Goldman, M. J.: Am. Heart J. **40**:93, 1950.
3. Goldman, M. J.: Am. J. M. Sc. **222**:382, 1951.
4. Miller, G., Weinberg, S. L., and Pick, A.: Circulation **6**:41, 1952.

NUCLEOTIDE LEVELS IN HUMAN CARDIAC MUSCLE

WALTER J. BURDETTE, PH.D., M.D.*

LONDON, ENGLAND

THE chemical events during contraction of cardiac muscle are of sufficient interest to justify inquiry into the quantitative relationships of those compounds involved in transfers of energy associated with contraction. In this connection the determination of nucleotides in human muscle would seem to provide especially useful information, and a series of studies have been carried out to obtain the desired data. When auricular muscle was obtained at the time of cardiotomy and fractions of homogenate were separated by ion-exchange columns, it was found that sufficient quantities of nucleotides were recovered to yield a fairly consistent quantitative picture. The results obtained with samples from 10 hearts are reported.

METHODS

The principles of anion exchange chromatography described by Cohn[1] and the system devised by Hurlbert and associates[2] and Potter and associates[3] were utilized in separating nucleotides from acid extracts of fresh, homogenized, human myocardium. Samples were obtained from 9 female patients at the time of valvotomy for mitral stenosis and from 1 (Sample 3) with mitral insufficiency. The average age of the patients was 35 years, with ages ranging from 23 to 45 years. Seven of the patients (Samples 1, 2, 3, 6, 7, 8, and 9) were digitalized at the time of surgery and 2 were fibrillating (Samples 1 and 6). Curare and Pentothal Sodium were administered to the first 8 patients and cyclopropane and ether to the last 2. One patient (Sample 3) died on the third day after a pericardial sling was inserted for the treatment of mitral insufficiency. The remaining patients left the hospital in good condition.

TABLE I. FORMIC ACID SYSTEM

H COOH N	NH_4 COOH M	NUMBER OF TUBES	H COOH N	NH_4 COOH M	NUMBER OF TUBES
0.005	0.0	5	2.2	0.0	3
0.05	0.0	6	2.5	0.0	5
0.2	0.0	8	3.0	0.0	6
0.6	0.0	3	4.0	0.0	3
1.0	0.0	3	4.0	0.05	6
1.5	0.0	7	4.0	0.15	4
1.7	0.0	7	4.0	0.3	6
2.0	0.0	3	4.0	2.0	5

From the Chester Beatty Institute for Cancer Research, and the Brompton Hospital, London, England.

Aided by a grant from the National Institutes of Health, Department of Health, Education, and Welfare, U.S.P.H.S., Bethesda, Md.

Received for publication June 28, 1957.

*Present address: Department of Surgery, St. Louis University School of Medicine, St. Louis, Mo.

The muscle was immediately immersed in cold saline when it was excised. After it was weighed, the cold tissue was homogenized in 0.5N perchloric acid. The neutralized supernatant was then placed on a simple, formate, ion-exchange hand column (Fig. 1). After this sample was placed on a column prepared from Dowex X-10, 200 to 400 mesh resin, the solutions listed in Table I were added in succession and 5 ml. fractions collected separately. Optical densities at 260 and 275mμ were determined, utilizing a model DU Beckman spectrophotometer, from which quantitative estimates of nucleotide fractions were made. In 2 of the samples, the adenosine nucleotide fractions were lyophilized, separately replaced on columns, and the eluents shown in Table II were passed through each (Figs. 2, 3, and 4).

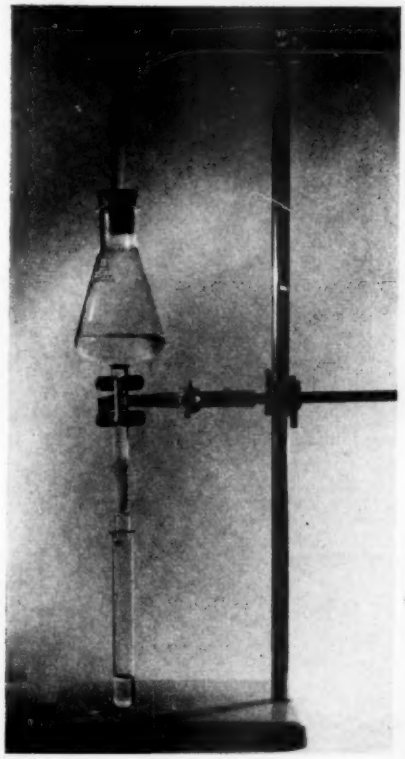


Fig. 1.—The simple hand column which was used in the study.

TABLE II. AMMONIUM FORMATE SYSTEM

NH_4 COOH M	NUMBER OF TUBES	NH_4 COOH M	NUMBER OF TUBES	NH_4 COOH M	NUMBER OF TUBES
0	4	0.40	5	0.75	5
0.05	4	0.45	5	0.80	5
0.15	4	0.50	7	0.85	5
0.20	4	0.55	7	0.90	5
0.23	4	0.60	5	1.0	4
0.25	4	0.63	5	1.2	5
0.30	4	0.65	5	1.3	7
0.35	5	0.67	5	1.5	4
0.38	5	0.70	5	2.0	3

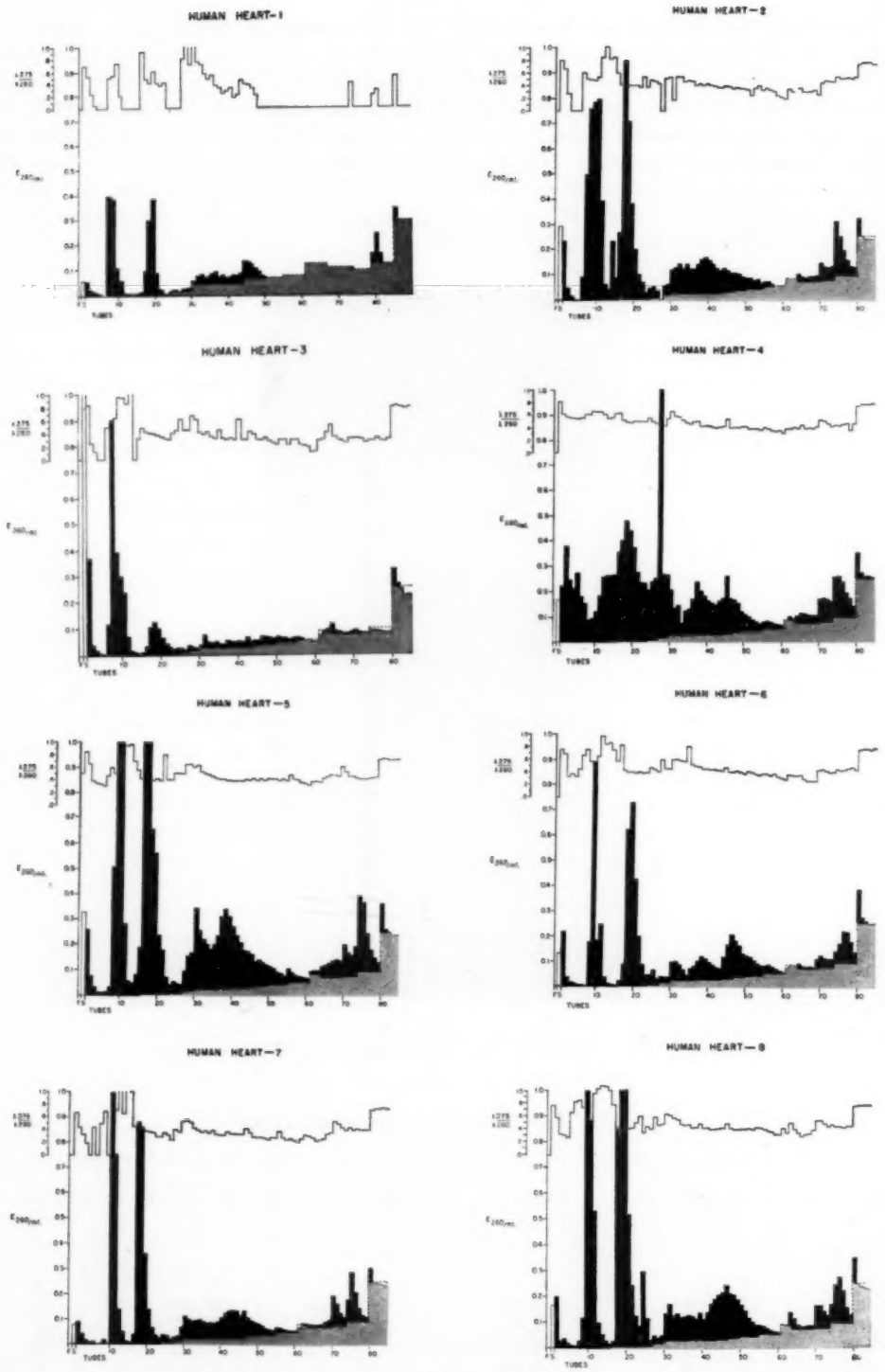


Fig. 2.—The spectrophotometer reading (E_{260}/ml.) of samples from homogenates of human hearts (1-8). Eluents were those of the formic acid system. Shaded area represents the absorption due to formic acid and ammonium formate. The *F* fraction is the density of aqueous washings of the prepared column, and the *S* fraction is the density of the initial liquid recovered when the sample is placed on the column. The ratio E_{275}/E_{260} is approximately 0.4 for adenosine nucleotides, 0.6 for uridin nucleotides, 0.75 for guanosine nucleotides, and 1 to 2 for cytosine nucleotides.[1-4]

RESULTS

The average, total amount of acid-soluble nucleotides extracted was 25.6 ± 1.7 M × 10^{-4} per gram wet weight of auricular muscle. The appearance of the graphs of optical densities may be found in Figs. 2, 3, and 4, and the amounts of adenosine nucleotides determined are recorded in Table III. The adenosine nucleotide fractions were identified by using the two systems of eluents (Tables I and II) and comparing the position of each fraction to that of known samples of adenosine monophosphate (AMP), adenosine diphosphate (ADP), and adenosine triphosphate (ATP) obtained from commercial sources. The average amount

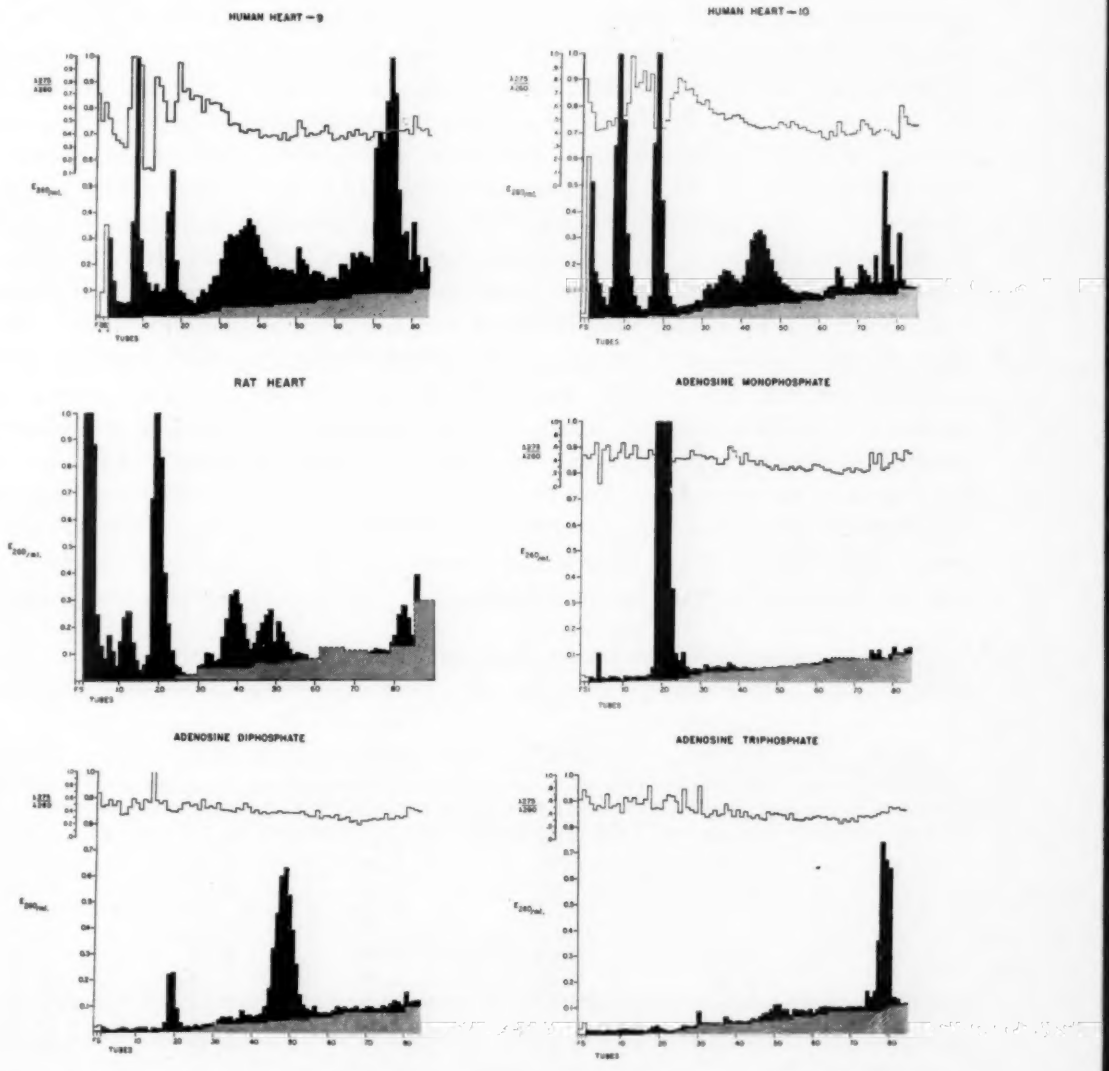


Fig. 3.—Spectrophotometer readings (E_{260}/ml.) of samples from homogenates of human hearts (9-10), myocardium of the rat, and known samples of the adenosine nucleotides from yeast. The sample of ADP is contaminated considerably with AMP. Eluents were those of the formic acid system.

of AMP found was 6.6 ± 0.8 M × 10^{-4} per gram; the average quantity of ADP was 3.3 ± 0.4 M × 10^{-4} per gram; and the mean value of ATP was 2.8 ± 0.6 M × 10^{-4} per gram wet weight.

DISCUSSION

Peaks of absorption for the eluate were fairly constant in relation to constitution of eluent, and relative concentration of various nucleotides was consistent enough to justify confidence in the reliability of the procedure. The fractions from human myocardium were similar in position to those obtained when optical densities of fractions from the ventricle of the rat and dog[1] and auricle of the dog were determined, but differences in constitution were noted when these values for the myocardium were compared to other tissues such as liver.[2] No correlation was found between the amount of specific nucleotides in various samples and the age of the patient from whom the tissue was taken, the presence of fibrillation, or the administration of digitalis. The fact that the sample from the only patient expiring in the postoperative period also contained the smallest amount of ATP is interesting. The ratio ATP:ADP:AMP in the study was 1.0:1.2:2.4, whereas ATP was more abundant (2.6 times) than AMP in similar studies on canine auricular muscle. Also, the content of adenosine nucleotides in the canine ventricle was approximately 3 times that in the auricle. An advantage of the gradient elution[5] system used is that it reveals a spectrum of acid-soluble nucleotides rather than isolating selected compounds, and examination of Figs. 2 and 3 verifies the presence of nucleotides other than the adenosine system. Cytosine, uridin, and possibly guanosine nucleotides are probably among those present. Functions similar to those of the adenosine nucleotides would seem a reasonable assumption. Recent evidence that the enthalpy change of ATP hydrolysis is much smaller than previously reported[6] gives added significance to the presence of other systems which may contribute to the energetics of contraction. Also, they may not only act as coenzymes but may also contribute to protein synthesis as well. The results obtained (Table III) confirm the presumed,

TABLE III. NUCLEOTIDE CONTENT OF HUMAN CARDIAC MUSCLE

HEART NUMBER	SAMPLE WEIGHT (GRAMS)	AMP*	ADP*	ATP*	TOTAL NUCLEOTIDE*
1	0.530	5.83	2.62	1.63	23.45
2	1.655	6.90	3.02	1.58	22.25
3	0.631	2.50	0.36	0.00	19.58
4	2.251	4.44	2.00	1.07	20.54
5	2.694	10.02	4.09	1.44	25.11
6	0.926	8.09	4.08	1.62	27.82
7	0.947	9.58	3.99	2.18	28.77
8	2.084	10.29	3.24	0.11	25.18
9	1.636	3.64	5.69	13.22	39.30
10	1.947	4.81	4.25	1.99	24.22
Mean	1.530	6.60±0.84	3.33±0.44	2.76±0.63	25.62±1.68

*M × 10^{-4} per gram wet weight.

prominent role of adenosine nucleotides in phosphate-bond exchange of energy during contraction of the human myocardium and demonstrate the feasibility of direct investigations on fresh muscle in man as a supplement to indirect methods and studies on animals.

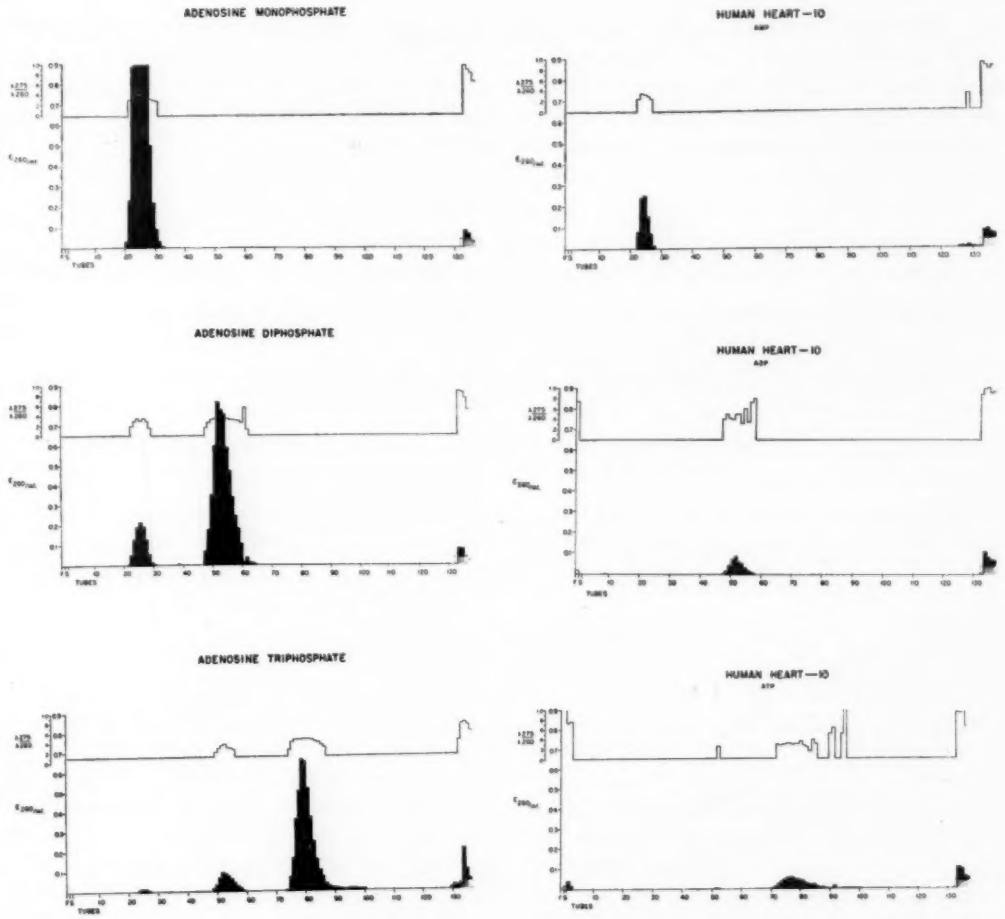


Fig. 4.—The lyophilized fractions of AMP, ADP, and ATP from the formic acid-ammonium formate separations of Sample 10 were placed on columns and recovered by means of the ammonium formate system. They are compared to known samples of AMP, ADP, and ATP from commercial sources in this figure. The commercial preparation of ADP also contains AMP, and that of ATP contains both AMP and ADP.

CONCLUSIONS

1. Acid-soluble nucleotides are present in human cardiac muscle in quantity sufficient for measurement in the amount of myocardium provided by an auricular biopsy.

2. The distribution of these fractions is similar for the myocardium of man, dog, and rat.

3. The average amounts of adenosine monophosphate, adenosine diphosphate, and adenosine triphosphate were 6.6, 3.3, and 2.8 M $\times$ 10^{-4} per gram, respectively.

4. A number of other nucleotides were also present in the samples. This suggests that the adenosine system is not the only one involved in protein synthesis and energy transfers responsible for contraction of the human myocardium.

The author wishes to express appreciation to Professor Alexander Haddow, who made the study possible; to Drs. J. A. V. Butler and Edna Roe in whose laboratory the work was done; to Sir Russell Brock, Sir Clement Price-Thomas, Mr. O. S. Tubbs, and Mr. W. P. Cleland for a portion of the auricular appendages supplied from their respective services at the Brompton Hospital; and to his wife for assistance with the technical procedures.

REFERENCES

1. Cohn, W. E.: Ann. N.Y. Acad. Sc. **57**:204, 1953.
2. Hurlbert, R. B., Schmitz, H., Brumm, A. F., and Potter, V. R.: J. Biol. Chem. **209**:23, 1954.
3. Schmitz, H., Hurlbert, R. B., and Potter, V. R.: J. Biol. Chem. **209**:41, 1954.
4. Burdette, W. J.: Am. Heart J. **52**:193, 1956.
5. Tiselius, A.: Endeavour **11**:5, 1952.
6. Podolsky, R. J., and Morales, M. F.: J. Biol. Chem. **218**:945, 1956.

BASE LINE FOR LEFT HEART CATHETERIZATION

SUJOY B. ROY, M.D.,* HOWARD L. GADBOYS, M.D.,** AND JAMES W. DOW, M.D.***

BOSTON, MASS.

THE left atrium has been punctured and the atrium and ventricle catheterized in several hundred patients by various groups.[1-13] The principal routes employed have been transbronchial and transthoracic.[1,2,3] Studies have been performed with the patients lying on either side, prone, supine, and erect.[3,7,9] Base lines employed for pressure registration have been the tip of the needle in the left atrium,[8] the mid-frontal plane,[10] and a point 5 cm. dorsad to the sternal angle of Louis[4] when stated. A few observations have been made in patients with normal hearts.[12]

Such a diversity of techniques, positions, and base lines makes comparison of the data reported by different groups difficult, and observations made in patients with heart disease provide no basis for estimating a normal range. The purpose of this paper is (1) to relate left atrial and ventricular diastolic pressures recorded supine and lying on the right side, (2) to suggest a basis for judging the normality or deviation from normal of such pressures, and (3) to discuss some considerations pertinent to selection of a reference plane for such studies.

METHOD AND MATERIAL

The first 29 left heart catheterizations performed in this laboratory form the basis for the study. The material is supplemented by somatic and x-ray chest measurements of 11 patients for whom left heart catheterization was contemplated but not done. The right hearts were catheterized in all 29 patients, and simultaneously with the left heart study in 14 of the 29. Thirteen of the 15 separate right heart studies were done in this laboratory. The results of the remaining two studies were made available to us by the staffs of the laboratories where the catheterizations were done. All patients were suspected of having valvular heart disease.

X-ray films were made of the hearts of all patients. The series included a right lateral view erect with barium swallow at a tube-film distance of 180 cm., and anteroposterior views in both lateral decubiti at 120 cm. The left atria usually appeared as denser areas within the heart shadows in the frontal view. An estimate of atrial configuration in lateral projection was based upon the size of the chamber and its impression on the esophagus. Smaller atria were assumed to be ovoid, larger ones to approach the spherical.[14] The chambers were not opacified.

From the Tufts Medical Services and Circulation Laboratory, Boston City Hospital; the Department of Medicine, Tufts University School of Medicine; and the Third (Boston University) Surgical Service and Research Laboratory, Boston City Hospital, Boston, Mass.

Supported by grants from the National Heart Institute (HT5012-C3) and the Massachusetts Heart Association.

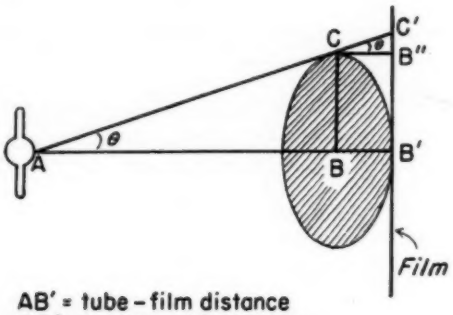
Received for publication July 4, 1957.

*Instructor in Medicine, Tufts University School of Medicine, and Research Fellow, Circulation Laboratory, Boston City Hospital.

**Research Assistant in Surgery, Third (Boston University) Surgical Service and Research Laboratory, Boston City Hospital. Research Fellow, National Heart Institute.

***Assistant Professor, Department of Medicine, Tufts University School of Medicine, and Physician-in-Charge of Circulation Laboratory, Boston City Hospital.

The position of the left atrium was outlined and its center located in each view. The distances from the centers of the atria to backs and dependent chest walls were measured on the films. The figures were corrected for magnification at the tube-film distances used before being compared with one another (Fig. 1). The ratios of the distances of left atria to backs over the anteroposterior diameters at the levels of the fourth costochondral junctions were calculated from the lateral views without correction in 17 patients. All films were made in full, held inspiration.



AB' = tube – film distance
BB' = half the object depth
BC = " " " width
$B''C'$ = " " " magnification

$$\frac{BC}{AB} = \tan.\theta = \frac{B''C'}{BB'}$$

$$B''C' = \frac{BC \cdot BB'}{AB}$$

Fig. 1.—Magnification of ellipsoid object on x-ray film. Dimensions CB and BB' are equal to ½ the somatic chest width and thickness, respectively, and are known. ACC' is a straight line and CB'' is parallel and equal to BB'. Angle θ and tangent θ are therefore equal for large and small triangles. The magnification $C'B''$ may be found in terms of the known values for AB, BC, and BB'.

Chest thicknesses at the second and fourth costochondral junctions and chest widths at the second costochondral junction were measured in 22 of the studied group and in 8 others. Elevations above the table top equal to ½ chest thicknesses measured at second and fourth costochondral junctions with patients erect were tentatively chosen as reference planes. Left atrium to back distances were calculated in 16 patients from the ratio left atrium to back over the anteroposterior diameter determined by lateral x-ray times the somatic chest thickness at the level of the atrium and the fourth costochondral junction. The elevation of the spinous process of the eighth vertebra above the table top in right lateral position was measured in 19 patients. All somatic and hemodynamic measurements were made during easy respiration.

The needle was inserted over the eighth or ninth rib 3.0 to 3.5 cm. to the patient's right of the eighth spinous process and passed at a shallow angle to the patient's left into the left atrium. The atria in all were punctured at a needle depth of 9 to 12 cm. and at a point near the midline of the spine. The technique of puncture will be reported separately.[15]

Left atrial pressure was recorded by direct puncture in all 29 patients studied. In 15 of these the pressure was recorded in supine and right lateral positions, and in one patient (W. H.) records were made in supine and both lateral decubiti. In 2 other patients indirect left atrial pressure tracings were made with catheters wedged far out in the right lung field in all three positions (Fig. 5). Left ventricular diastolic pressure was recorded in 17 patients. These recordings were made in the supine as well as right lateral position in 6. Pulmonary arterial pressures were recorded in supine and right lateral positions in 14 patients. The surface on which the patients lay was the base line for all pressures.

RESULTS

Anatomic Relations.—

Somatic measurements: The chest dimensions are tabulated in Table I. Although the width of the chest exceeds its thickness at the fourth costochondral junction by a ratio of 6 to 5, the dependent chest is compressed with the subject lying on the right side so that the elevation of the midline of the spine from the table top is nearly equivalent to ½ the chest thickness at the fourth costochondral junction.

TABLE I. SOMATIC CHEST MEASUREMENTS

NUMBER	PATIENT	CHEST THICKNESS (MM.)		CHEST WIDTH AT 2ND COSTOCHONDRAL JUNCTION (MM.)	8TH SPINOUS PROCESS TO TABLE TOP IN RIGHT LATERAL POSITION (MM.)
		2ND COSTOCHONDRAL JUNCTION	4TH COSTOCHONDRAL JUNCTION		
1.	J.P.	185	205	245	100
2.	D.H.	180	190	260	105
3.	R.M.				
4.	S.H.	230	245	285	120
5.	M.R.	210		235	105
6.	L.H.	195	210	235	100
7.	E.O'L.	185		225	120
8.	L.M.	210	220	260	100
9.	K.B.	223		255	
10.	E.M.	160	180	270	90
11.	J.Q.	225	235	260	120
12.	T.E.	205	225	265	130
13.	H.T.	210			
14.	R.B.	250			
15.	E.D.	220	240	250	90
16.	F.P.	180	210	300	100
17.	N.H.	180	195	270	100
18.	T.N.	215	220	295	120
19.	A.L.	165	182	265	100
20.	E.C.	165	185	275	90
21.	B.B.	215	230	260	100
22.	M.D.	160	170	225	90
23.	L.G.	250	260	325	101
24.	P.W.	190	215	275	105
25.	J.C.	215	230	305	105
26.	E.M.	205	235	285	98
27.	P.C.	200	210	285	103
28.	H.R.	180	200	255	95
29.	W.H.	205	215	250	96
30.	Y.B.	163	180	260	
31.	D.L.	185	195	270	98

Radiographic measurements: The left atria center over the midlines of the spines in the frontal view with the subjects erect and supine. The heart becomes more dependent in either lateral position so that the atrial midline usually approximates the inferior margin of the vertebral bodies.[15] The left atria therefore rest 1.0 to 1.5 cm. lower than the level of the midline of the spine in the lateral positions.

The left atria are located close to the centers of the anteroposterior chest axes at the levels of the fourth costochondral junctions with the patients erect (Table II). This relation is not altered in the supine. The distances from left atrial centers to backs, determined by multiplying the ratio LA/CT taken from

TABLE II. LOCATION OF THE LEFT ATRIAL CENTER ON THE ANTEROPOSTERIOR CHEST AXIS BY LATERAL X-RAY

NUMBER	PATIENT	CHEST THICKNESS AT LEVEL OF LEFT ATRIUM (4TH COSTOCHONDRAL JUNCTION) IN MM.	LEFT ATRIAL CENTER TO BACK IN MM.	RATIO LEFT ATRIUM TO BACK/CHEST THICKNESS
2.	D.H.	236	125	.530
4.	S.H.	285	135	.473
8.	E.O'L.	226	110	.487
10.	K.B.	225	109	.484
11.	E.M.	208	98	.471
13.	T.E.	254	130	.512
17.	R.B.	270	127	.470
24.	T.N.	242	130	.537
25.	A.L.	200	111	.556
26.	G.C.	199	109	.548
28.	M.D.	188	97	.516
29.	L.G.	265	128	.483
30.	A.M.	235	118	.502
31.	P.W.	268	127	.474
35.	H.R.	253	114	.451
36.	W.H.	250	115	.460
37.	D.L.	235	122	.519
			Average	.513
			Range	.451—.556

Film distances not corrected for magnification. X-rays taken with patients erect in held inspiration.

TABLE III. COMPARISON OF DISTANCE FROM LEFT ATRIUM TO BACK, SPINOUS PROCESS TO TABLE TOP, AND ONE HALF OF CHEST THICKNESS AT SECOND AND FOURTH COSTOCHONDRAL JUNCTIONS

NUMBER	PATIENT	LEFT ATRIUM TO BACK WITH PATIENT ERECT (MM.)	SPINOUS PROCESS TO TABLE IN RIGHT DECUBITUS (MM.)	ONE HALF THICKNESS AT 4TH COSTOCHONDRAL JUNCTION WITH PATIENT ERECT (MM.)	ONE HALF THICKNESS AT 2ND COSTOCHONDRAL JUNCTION WITH PATIENT ERECT (MM.)
2.	D.H.	109	105	95	90
4.	S.H.	116	120	123	115
11.	E.M.	85	90	90	80
13.	T.E.	115	130	113	103
24.	T.N.	118	120	110	108
25.	A.L.	101	100	91	83
26.	G.C.	101	90	93	83
28.	M.D.	88	90	85	80
37.	H.R.	90	95	100	90
38.	W.H.	99	96	108	103
40.	D.L.	101	98	98	93
Average		102.1	103.0	100.4	93.5

lateral films by the somatic thicknesses at the fourth costochondral junctions, correspond with the figures for ½ the chest thickness at that level and with elevations of spinous processes from the table tops (Table III). The actual elevation of the left atrium above the table top is about 1 cm. less than the calculated distance from left atrium to back because the chest is flattened in the supine position (Table IV). This elevation is more nearly equivalent to ½ the chest thickness at the second rather than at the fourth costochondral junction.

TABLE IV. COMPARISON OF CHEST THICKNESSES AT SECOND AND FOURTH COSTOCHONDRAL JUNCTIONS IN ERECT AND SUPINE POSITIONS

NUMBER	PATIENT	CHEST THICKNESS (MM.)			
		2ND COSTOCHONDRAL JUNCTION		4TH COSTOCHONDRAL JUNCTION	
		ERECT	SUPINE	ERECT	SUPINE
2.	D.H.	180	172	190	175
35.	H.R.	180	180	200	190
36.	W.H.	205	200	215	200
37.	Y.B.	163	160	180	165
38.	D.L.	185	180	195	185

Chest flattening on shift from erect to supine position is greater at the fourth than at the second costochondral junction.

TABLE V. CORRECTED X-RAY DISTANCES FROM LEFT ATRIAL CENTER TO DEPENDENT SIDE IN BOTH LATERAL DECUBITI AND TO BACK WITH PATIENT ERECT

NUMBER	PATIENT	LEFT ATRIUM TO BACK (MM.)	LEFT ATRIUM TO TABLE TOP	
			ON RIGHT SIDE	ON LEFT SIDE
1.	J.P.	93	94	97
2.	D.H.	122	134	142
4.	S.H.	124	132	134
8.	E.O'L.	104	118	118
10.	K.B.	101	84	102
11.	E.M.	91	99	104
12.	J.Q.	111	128	129
13.	T.E.	118	135	124
14.	H.T.	131	131	135
19.	E.D.	141	138	136
22.	F.P.	136	151	146
23.	N.H.	117	122	128
24.	T.N.	120	125	137
25.	A.L.	104	120	106
26.	G.C.	101	118	110
28.	M.D.	91	97	93
29.	L.G.	118	127	115
30.	P.W.	117	126	116
Average		113.2	120.9	120.4

Left atrium to back corrected for magnification at tube-film distance of 180 cm., and to dependent side corrected for distance of 120 cm.

The x-ray distances of the left atria from the dependent chest walls in the two lateral decubiti agree well (Table V). These figures exceed the distances from atria to back in lateral views but, when individually corrected for magnification with known somatic dimensions and shorter tube-film distances in the lateral decubitus positions, agreement is fairly close.

Correlated x-ray and somatic measurements indicate that the left atria are at almost identical elevations in supine and both lateral decubitus positions (Fig. 2). This level is most nearly approximated by a distance above the table top equal to ½ chest thickness at the second costochondral junction measured with the patient recumbent in easy expiration. These measurements are less than the corrected distances from atrial centers to backs and to dependent sides determined on the x-ray films. Since the films were made in the inspiratory phase, the figures based primarily upon somatic measurements with x-rays serving only to locate the positions of the atria with relation to bony chest structures more nearly represent the anatomic relationships during hemodynamic studies.

Vertical displacement of chamber in relation to reference plane is recorded as a pressure difference. The magnitude of such displacements of the left atria from

TABLE VI. HYDROSTATIC DIFFERENCES FROM LEFT ATRIAL LEVEL FOR REFERENCE PLANES AT ONE HALF CHEST THICKNESSES AT SECOND AND FOURTH COSTOCHONDRAL JUNCTIONS, STERNAL ANGLE MINUS 5.0 CM., AND THE BURWELL LEVEL

NUMBER	PATIENT	L.A. TO BACK (MM.)	ONE HALF CHEST THICKNESS AT 2ND COSTO-CHONDRAL JUNCTION (MM.)		ONE HALF CHEST THICKNESS AT 4TH COSTO-CHONDRAL JUNCTION (MM.)		STERNAL ANGLE LESS 50 MM.		BURWELL LEVEL (100 MM. ABOVE TABLE TOP)	
			LEVEL	ERROR	LEVEL	ERROR	LEVEL	ERROR	LEVEL	ERROR
2.	D.H.	109	90	+19	95	+14	130	−21	100	+9
4.	S.H.	116	115	+1	123	−7	180	−64	100	+16
11.	E.M.	85	80	+5	90	−5	110	−25	100	−15
13.	T.E.	115	103	+12	113	+2	155	−40	100	+15
24.	T.N.	118	108	+10	110	+8	165	−47	100	+18
25.	A.L.	101	83	+18	91	+10	115	−14	100	+1
26.	G.C.	101	83	+18	93	+8	115	−14	100	+1
28.	M.D.	88	80	+8	85	+3	110	−22	100	−12
35.	H.R.	90	90	0	100	−10	130	−40	100	−10
36.	W.H.	99	103	−4	108	−9	155	−56	100	−1
38.	D.L.	101	93	+8	98	+3	135	−34	100	+1
Average				+9		+1		−38		+2
Range				+19 −4 23		+14 −10 24		−14 −64 50		+18 −15 33

The standard of left atrium to back used is probably about 1 cm. too large owing to flattening of the chest in the supine. Variability is the same for the mid-frontal planes at the second and fourth costochondral junctions, greater for the Burwell level, and greatest for a level referred to the anterior chest only. A smaller figure for the distance left atrium to back in the supine brings the chamber into line with an elevation above the table top equal to ⅓ chest thickness at the second rather than the fourth costochondral junction.

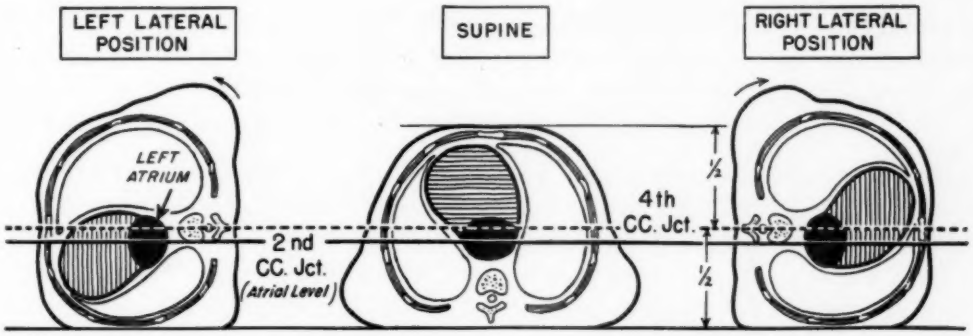


Fig. 2.—Left atrial elevation in relation to the mid-frontal planes at second and fourth costochondral junctions in right and left lateral positions. The center of the left atrium is in line with the lower margin of the spine in both lateral positions, and at the same elevation with the patient supine. In all positions the distance from left atrial center to table top is approximately equal to ½ the thickness of the chest at the second costochondral junction.

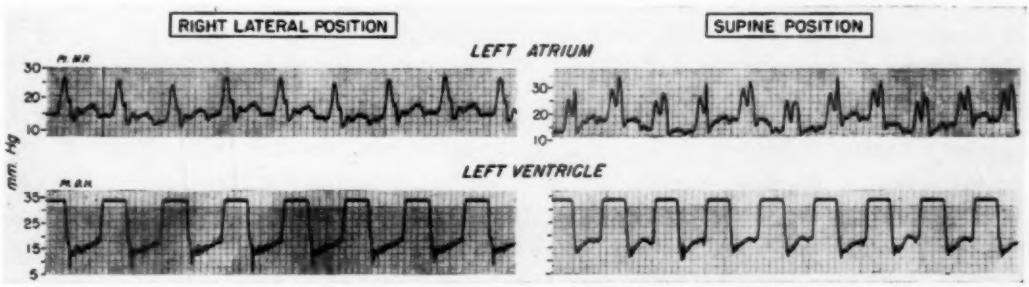


Fig. 3.—Consecutive left atrial and left ventricular diastolic pressures in right lateral and supine positions. Shifting from right lateral to supine position produces only minor changes in pressure forms.

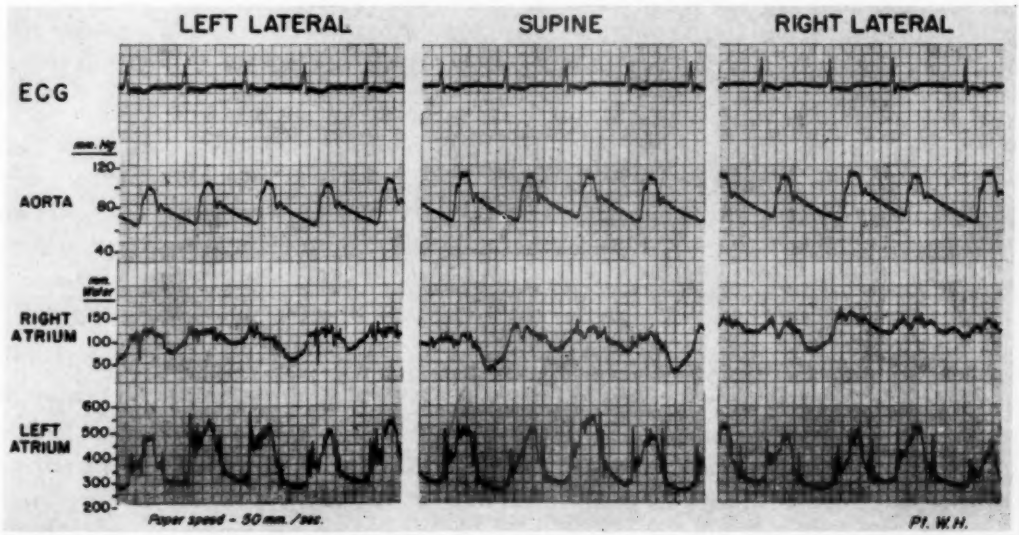


Fig. 4.—Right and left atrial pressures in supine and both lateral decubitus positions. Directly recorded left atrial pressures are identical with the subject supine or lying on either side.

TABLE VII. HEMODYNAMIC DATA: BASE LINE—TABLE TOP (PRESSURES IN MM. Hg)

SERIAL NUMBER	PATIENT	LEFT ATRIUM (MEAN)			LEFT VENTRICLE (DIASTASIS)			PULMONARY ARTERY (MEAN)		
		SUPINE	RIGHT DECUBITUS	DIFFERENCE	SUPINE	RIGHT DECUBITUS	DIFFERENCE	SUPINE	RIGHT DECUBITUS	DIFFERENCE
1.	J.P.	31	33	+2	—	24	—	40	40	0
2.	D.H.	27	27	0	20	20	0	38	37	−1
3.	R.M.	—	24	—	—	12	—	41	37	−4
4.	S.H.	—	43	—	—	22	—	59	63	+4
6.	M.R.	20	20	0	18	16	−2	29	—	—
7.	L.H.	26	26	0	18	—	—	—	—	—
9.	L.M.	16	18	+2	18	20	+2	32	30	−2
11.	E.M.	23	23	0	—	—	—	50	50	0
12.	J.Q.	30	29	−1	10	10	0	66	—	—
14.	H.T.	40	40	0	—	—	—	80	80	0
15.	W.D.	—	18	—	16	—	—	28	30	+2
22.	F.P.	23	23	0	21	21	0	27	—	—
29.	L.G.	—	25	—	—	23	—	28	30	+2
33.	P.W.	30	30	0	14	13	−1	48	50	+2
34.	J.C.	22	22	0	—	21	—	38	38	0
35.	E.M.	26	26	0	—	11	—	38	—	—
36.	P.C.	36	36	0	—	18	—	37	37	0
37.	H.R.	35	35	0	—	25	—	47	47	0
38.	W.H.	36	34	−2	—	14	—	47	47	0
Average				+0.06			−0.17			+0.21

planes at levels equal to ½ chest thickness at second and fourth costochondral junctions, from a plane passing 5.0 cm. dorsad to the sternal angle of Louis, and from one 10. cm. ventrad to the back (Burwell level) are indicated in Table VI. Variability is least when the mid-frontal planes are employed.

Pressure measurements: Left atrial and ventricular diastolic pressures do not differ consistently when measured with the subject lying supine or on the right side (Table VII and Fig. 3). In most instances the pressures are not measurably changed. Left atrial pressures recorded both directly (Fig. 4) and indirectly (Fig. 5) are identical with the patients in left and right lateral decubiti. Pulmonary vascular pressures are not affected by location of the recording orifice in elevated or dependent lung (Figs. 5 and 6).

DISCUSSION

All pressure measurements made within a vascular system must be related to a common base line if they are to be compared. It would be incorrect, for example, to compare right atrial pressure measured against one frame of reference with left atrial pressure measured against a second, even if these two chambers were at widely different levels.

A variety of reference planes have been suggested for venous pressure measurement[16-20] and later adopted for right heart catheterization. Since each of these planes was intended to pass through the center of the right atrium, the pressure discrepancy that results from using one rather than another rarely amounts to more than a few mm. Hg. Placement of the reference plane at the level of the chamber in question is meaningful only provided both chamber and plane are at the same environmental pressure, or if the environmental pressure differences are minimal, constant, or known. For intracardiac pressures this is not the case, the heart being enclosed under negative pressure in the chest. Since intrapleural negativity is affected by lung compliance and ventilatory volume and is impractical to measure routinely, it cannot either be assumed to be constant or used directly as a reference.

Even if it were measurable or were reliably related to intraesophageal pressure, intrapleural pressure is a valid reference level only when the pericardium exerts no confining force upon the heart during diastolic filling. The pericardium does so confine the experimentally dilated heart,[21] and may confine the hearts of patients selected for transthoracic atrial puncture. An ideal external reference plane therefore is not attainable.

If absolute pressure relationships cannot be determined, the most that can be hoped for is consistency and convenience in measurement. A base line that passes through the center of a chamber eliminates hydrostatic pressure differences so that the scatter of observations made in normal subjects of different sizes will be minimized. For the left atrium a mid-frontal plane at the second costochondral junction approximates such a base line in supine and both lateral positions. Predictable hydrostatic error with this base line will usually amount to less than 1 mm. Hg.

Although reference to the mid-frontal plane at the second costochondral junction minimizes hydrostatic variability within a group of subjects, variability due to change of position in a given subject is neither greater nor less with this reference level than in relation to any other fixed base line. The fact that the left atrium is at nearly constant elevation in supine and both lateral positions means that no important pressure change due to altered height of the chamber is introduced whatever base line is used.

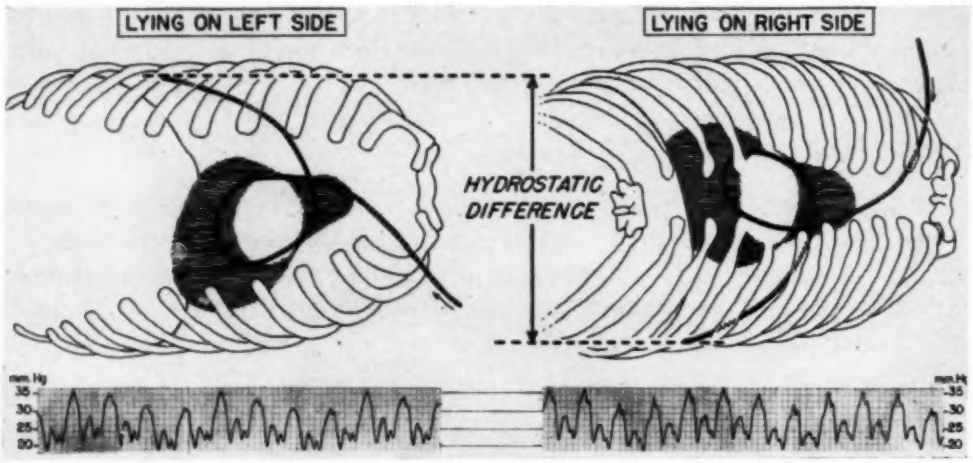


Fig. 5.—Wedge pressures in elevated and dependent lung. Indirectly recorded left atrial pressure is unaffected by the change from left to right decubitus, although the hydrostatic pressure acting on the catheter orifice is 15 mm. Hg greater with the subject on the right side.

Use of a mid-frontal plane requires that the base line be adjusted for each procedure or that a correction be made later. A base line fixed in relation to the table top may be left unchanged for all procedures. The table top itself is a convenient level to reproduce and offers the advantage that all pressures are recorded as greater than atmospheric. The recorded pressure probably approximates the distending pressure of the heart more closely against this level than do those recorded against the higher reference planes. Variability during a given procedure is the same as for the other levels, and that within a group is the same as for the Burwell level, less than for level related to the anterior chest, but greater than for a mid-frontal plane.

These advantages of convenience and interpretation have led to the use of the table top as base line in this laboratory until now. The indicated gain in consistency when a mid-frontal plane is employed has caused us to adopt ½ the chest thickness, measured at the second costochondral junction with the subject supine in easy expiration, as the base line for future hemodynamic studies.

The right and left sides of the heart may and often should be catheterized simultaneously.[10] Since the venous catheter may be placed far out in either right or left pulmonary artery when the patient is turned to the right side, a 15 to 20 cm. range in vertical elevation of the tip above the table top is possible.

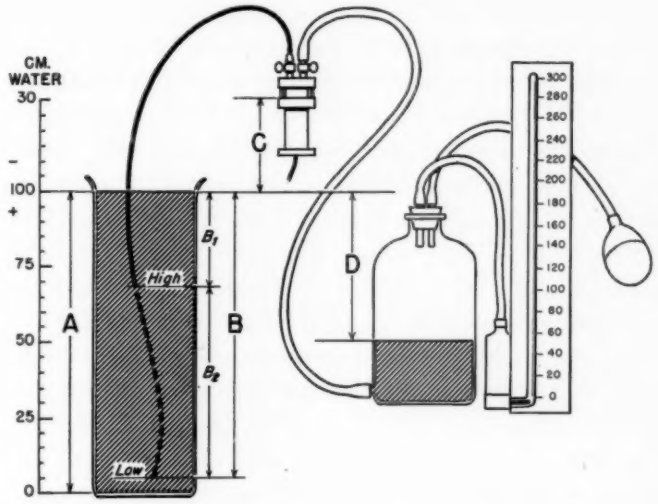


Fig. 6*A*.—When the transducer is open to the cylinder, the pressure acting on its diaphragm is 30 cm. of water less than atmospheric. When open to the reference level in the bottle, diaphragm pressure is 80 cm. of water below atmospheric. On switching from bottle to cylinder, pressure acting on the diaphragm rises 50 cm. of water, from −80 cm. to −30 cm. of water. Any change in the relative positions of the two levels alters the value (*D*) and is measured as a pressure change. The system is unaffected by the height of the water column (*A*), by the location of the catheter tip near the top of the column (B_1) or at the bottom (*B*). A change of manometer level alters only the position of the base line on the graphic recording.

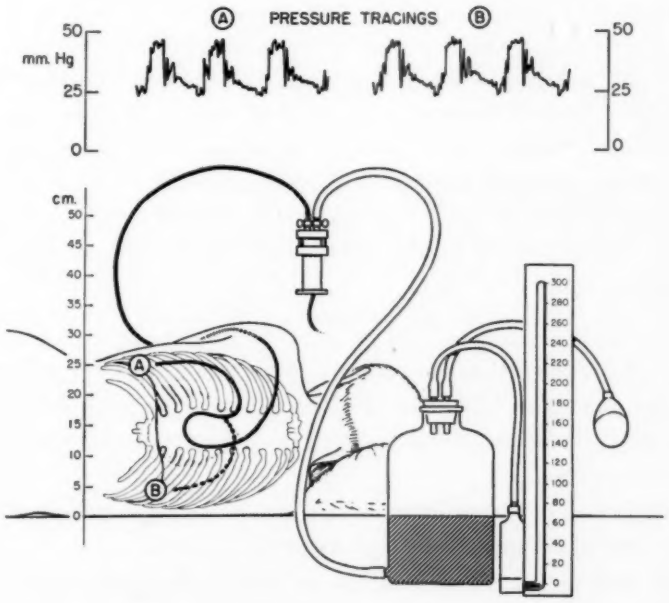


Fig. 6*B*.—The pulmonary vasculature is analogous to the cylinder of water above. The position of the catheter at (*A*) or (*B*), though sometimes equivalent to a hydrostatic difference of 20 mm. Hg, does not affect the recorded pressure.

A hydrostatic pressure difference equal to the weight of a column of blood of that height must act upon catheter tips in the extreme locations. At first glance it might seem that this vertical range of orifice placement would cause the pressure recordings made in the lateral decubiti to vary by an equivalent figure. Confusion on this point has appeared occasionally in published work.

In fact, the vertical elevation of the catheter tip is not recorded in a fluid system referred to a fixed base line (Fig. 6). Such hydrostatic differences would be detected by a transducer fixed to the catheter tip, a consideration that limits the potential usefulness of such a device. Changing the elevation of the catheter tip through the maximal possible vertical range by turning from left to right decubitus did not affect the recorded pressure (Fig. 5). Regardless of orifice placement one pressure difference only is recordable by such a system, the difference between the base line level and the pressure at which the fluid is contained in the vasculature (Fig. 6).

The concern over the constancy of left atrial elevation in the three positions studied is not inconsistent with the point that vertical displacement of catheter tip is not recorded as a pressure difference. A change in left atrial level would be equivalent to raising or lowering the cylinder and thereby changing the value (*D*) in Fig. 6*A* and not to the depth of immersion (*B*) of the catheter tip in the cylinder. Such a difference would of course be recorded as altered pressure.

Although some data have been collected,[12] catheterization of the left heart at present seems too formidable to employ for control data in subjects with normal circulations. Fortunately, the concept that pulmonary "capillary" pressure provides an indirect measure of left atrial pressure[22,23] has now been thoroughly validated.[24-27]

The pulmonary "capillary" pressures measured in "normal" subjects by Dexter afford a guide for the normality or deviation from normal of left atrial and left ventricular diastolic pressures in patients studied in either right lateral or supine positions.[28] Dexter's average normal figure was 9 mm. Hg, with a range from 6 to 12 mm. Hg using a base line 10 cm. above the supporting surface. Six of the 8 observations ranged from 6 to 9 mm. Hg. Since Dexter recorded chest thickness his figures may be converted to any reference level. In these 6 patients the figures are unchanged if a mid-frontal plane at the second costochondral junction is used.

SUMMARY

1. X-ray and somatic measurements show that the left atrium is at approximately the same elevation with the subject supine and lying on the right or the left side. The elevation is equal to ½ the chest thickness measured at the second costochondral junction.

2. Left atrial and ventricular diastolic pressures recorded in relation to any fixed base line are the same in all three positions.

3. A base line at an elevation above the table equivalent to ½ of chest thickness at the second or fourth costochondral junction minimizes variability of pressures recorded in subjects of different sizes. Hydrostatic error is probably least if the second costochondral reference level is used.

4. A base line fixed in relation to the table top offers some advantage in simplicity with no loss of meaning and little sacrifice of consistency from patient to patient. Chest dimensions and reference level should be stated to permit correlation with measurements made against any other base line.

5. Previously reported "normal" pulmonary "capillary" pressures provide a basis for judging the normality of left atrial and ventricular diastolic pressures measured with patients supine or lying on the right or left side.

6. Hydrostatic pressure differences are not recorded against a common base line. Vertical displacement of pulmonary arterial catheter tip introduces no problem in interpretation of pressure records.

We are indebted to Dr. Allan Friedlich of the Department of Cardiology at the Massachusetts General Hospital, and to Dr. Walter Abelman of the Heart Station at the Boston City Hospital for making available to us the results of right heart study in patients M. R. and R. B.

REFERENCES

1. Facquet, J., et al.: Arch. mal. coeur **45**:741, 1952.
2. Allison, P. R., and Linden, R. J.: Circulation **7**:669, 1953.
3. Björk, V. O., Malmström, G., and Uggla, L. G.: Ann. Surg. **138**:718, 1953.
4. Epps, R. G., and Adler, R. H.: Brit. Heart J. **15**:298, 1953.
5. Björk, V. O.: Acta chir. scandinav. **107**: Fasc. 5, 466, 1954.
6. Radner, S.: Acta med. scandinav. **151**:22, 1955.
7. Kent, E. M., et al.: Ann. Surg. **141**:47, 1955.
8. Fisher, D. L.: J. Thoracic Surg. **30**:379, 1955.
9. Lawrence, G. H., Zimmerman, H. B., Bercu, B. A., and Burford, T. H.: Surg., Gynec. & Obst. **101**:558, 1955.
10. Wood, E. H., Sutterer, W., Swan, H. J., and Helmholz, H. F., Jr.: Proc. Staff Meet. Mayo Clin. **31**:108, 1956.
11. Lawrence, G. H.: New England J. Med. **255**:180, 1956.
12. Bougas, J., Musser, B. G., and Goldberg, H.: Am. Heart J. **52**:359, 1956.
13. Musser, B. G., Bougas, J., and Goldberg, H.: Am. Heart J. **52**:567, 1956.
14. Dotter, C. T., and Steinberg, I.: Ann. Roentgen. **20**:87, 137, 1951.
15. Gadboys, H. L., Roy, S. B., and Dow, J. W.: Simplified Procedure for Combined Heart Study. Ann. Surg. (To be published.)
16. Moritz, F., and von Tabora, D.: Deutsch. Arch. f. klin. Med., Leipzig **98**:475, 1910.
17. Winsor, T., and Burch, G. E.: Proc. Soc. Exper. Biol. & Med. **58**:165, 1945.
18. Von Recklinghausen, H.: Arch. f. exper. Path. Pharmakol., Leipzig **55**:375, 1906.
19. Eyster, J. A. E.: The Clinical Aspects of Venous Pressure, New York, 1929, The Macmillan Company.
20. Lyons, R. H., Kennedy, J. A., and Burwell, C. S.: Am. Heart J. **16**:675, 1938.
21. Bergland, E., Sarnoff, S. J., and Isaacs, J. P.: Circulation Res. **3**:133, 1955.
22. Lagerlof, H., and Werkö, L.: Scandinav. J. Clin. & Lab. Invest. **7**:147, 1949.
23. Dow, J. W., and Gorlin, R.: Fed. Proc. **9**:33, 1950.
24. Calzel, P., et al.: Bull. Johns Hopkins Hosp. **88**:22, 1951.
25. Werkö, L., et al.: Circulation Res. **1**:337, 1953.
26. Wilson, R. H., et al.: J. Lab. & Clin. Med. **42**:408, 1953.
27. Connolly, D. C., Kirklin, J. W., and Wood, E. H.: Circulation Res. **2**:434, 1954.
28. Dexter, L., et al.: J. Clin. Invest. **29**:602, 1950.

ON METHODS AND COMPLICATIONS IN CATHETERIZATION OF HEART AND LARGE VESSELS, WITH AND WITHOUT CONTRAST INJECTION

MARIANNE BAGGER, M.D., G. BIÖRCK, M.D., V. O. BJÖRK, M.D., B. BRODÉN, M.D., L. E. CARLGREN, M.D., A. CARLSTEN, M.D., I. EDLER, M.D., B. EJRUP, M.D., H. ELIASCH, M.D., A. GUSTAFSON, M.D., Å. GYLLENSWÄRD, M.D., H. E. HANSON, M.D., A. HOLMGREN, M.D., H. IDBOHRN, M.D., S. R. JOHNSSON, M.D., B. JONSSON, M.D., G. JÖNSSON, M.D., J. KARNELL, M.D., S. R. KJELLBERG, M.D., H. KROOK, M.D., H. LARSSON, M.D., L. LINDÉN, M.D., E. LINDER, M.D., H. LINDERHOLM, M.D., H. LODIN, M.D., G. MALMSTRÖM, M.D., E. MANNHEIMER, M.D., T. MÖLLER, M.D., J. PHILIPSSON, M.D., S. RADNER, M.D., U. RUDHE, M.D., G. STRÖM, M.D., B. SÖDERHOLM, M.D., F. ULFSPARRE, M.D., AND L. WERKÖ, M.D.

STOCKHOLM, SWEDEN

THIS report describes experiences concerning methods and complications in catheterization of heart and large vessels, with and without contrast injection, acquired in 12 Swedish hospitals, in Stockholm, Göteborg, Malmö, Uppsala, and Lund.

Fatal Complications.—Table I shows the number of different examinations at the various hospitals, and the number of fatal complications. The latter are further described in Table II. Five deaths having obvious connection with the procedure of right heart catheterization occurred, mostly in the early years when this examination was being introduced. There were three additional fatal complications where the causal connection with catheterization was uncertain. The rate of certain fatal complications due to right heart catheterization is therefore 5/5,859. The corresponding figure for aortic catheterization (prior to thoracic aortographies) is 2/340. Angiocardiography, angiopulmography, and thoracic aortography is performed by the combined procedures of catheterization, general anesthesia, and contrast injection. In a total number of 2,958 such examinations there were 14 certain and 1 uncertain fatal complications; 3 certain complications occurred after general anesthesia had been induced, without contrast injection, and 9 after contrast injection had been performed; in the remaining 2 cases the fatal complication occurred during aortic-arch catheterization before anesthesia or contrast injection.

The 4 fatal cases of uncertain connection with the diagnostic procedure were patients in serious general condition, where the primary disease in itself gave sufficient indication of the outcome. They will not be analyzed in further detail below (cf. Table II).

Preliminary report given by G. Ström at the Second European Congress on Cardiology, Stockholm, 1956.

Received for publication July 11, 1957.

TABLE I. NUMBER OF DIFFERENT CATHETERIZATIONS AND ANGIOCARDIOGRAPHIC EXAMINATIONS AT 12 SWEDISH HOSPITALS*

Hospital number	1	2	3	4	5	6	7	8	9	10	11	12	1-12
Observation period	1948-55	1952-56	1947-56	1951-55	1947-55	1948-56	1951-56	1949-55	1952-55	1953-54	1953-56	1955-56	
RH cath.	1,200	700	892	632	467	467	595	304	240	158	148	56	5,859
LIV cath.						136		20					156
REV cath.								100					100
BRA cath.								300			179	234	713
Angioc.			253	500	20	167	116		12			8	1,076
Sel. angioc.			209	490	342	121	57		114	42			1,375
Thoracic aortographies					277	30	33						340
Angiopulmographies						167							167
Fatal cases, certain, (uncertain), total number	2	(1)	2 + (1)	5	5	4	(1)		1	(1)			19 + (4)
RH cath.	2	(1)		1		1	(1)		1	(1)			5 + (3)
RH cath. + anesth.				1	1								2
AA cath.					1	1							2
AA cath. + anesth.					1								1
RH cath. + anesth. + contrast inj.			2	3	1	1							7
AA cath. + anesth. + contrast inj.			(1)		1	1							2 + (1)

*Number of fatal complications (uncertain cases given in parentheses).

RH= right heart; AA= aortic arch; BRA= brachial artery; REV= renal vein; LIV= liver vein; cath.= catheterization; anesth.= anesthesia; inj.= injection; sel.= selective; angioc.= angiocardiography.

TABLE II. DESCRIPTION OF 19 CERTAIN FATAL COMPLICATIONS TO CATHETERIZATION AND ANGIOCARDIOGRAPHY, AND FOUR ADDITIONAL UNCERTAIN CASES*

CASE NUMBER	HOSPITAL NUMBER	AGE	SEX	DIAGNOSIS	EXAMINATION	TIME OF FATAL OUTCOME	CAUSE OF FATAL OUTCOME
1	1	60	M	Arterial hypertension, left bundle branch block	Venous cath. for renal clearance	Cath. tip in right atrium	Cardiac standstill
2	1	52	M	Aortic stenosis + unknown myocardial infarction	RH cath.	Cath. tip in right ventricle	Cardiac standstill
3	(2)			Pulmonary tuberculosis	RH cath.	Night after cath.	Serious general condition
4	3	7	M	Mb. coeruleus	RH cath. + angioc.	3 hr. after angioc.	Unconscious after angioc., heart failure
5	3	5	F	Mb. coeruleus	RH cath. + angioc.	3 min. after angioc.	Cardiac standstill, probably anesthetic complication
6	(3)			Kidney malformation	AA cath. + aortography	Several days after aortography	Serious general condition + arterial embolism
7	4	8	F	Fallot's tetralogy	RH cath.	24 hr. after cath.	Ventricular tachycardia + poor general condition
8	4	<1		Mitral atresia	RH cath. + repeated angioc.	Immediately after second angioc.	Cardiac standstill
9	4	7	F	V.S.D.	RH cath. + angioc.	10 min. after angioc.	Air embolism?
10	4	3	F	A-V commune	RH cath. + angioc.	10 min. after angioc.	Heart failure
11	4	<1		Fallot's tetralogy	RH cath. + anesth.	Before angioc.	Anesthetic complication

12	5	8	F	Fallot's tetralogy	RH cath. under anesth.	Cath. tip in right ventricle	Cardiac standstill
13	5	19	M	Aortic coarctation	AA cath. (cath. not radio-opaque)	Before aortography	Cardiac standstill
14	5	17	M	V.S.D. + aortic incompetence	AA cath. + anesth.	Before aortography	Anesthetic complication + heart failure
15	5	20	F	Pulmonary stenosis	Venous cath. + angioc.	Immediately after anesth.	Ventricular fibrillation
16	5	20	M	Aortic coarctation	Repeated AA cath. + aortography	Several days after second aortography	Anuria + septic thrombo-embolism
17	6	10	F	Superior vena cava duplex + Eisenmenger's complex	Venous cath.	Cath. tip in superior vena cava	Cardiac standstill
18	6	15	F	Aortic coarctation	AA cath., aortography intended	Several days after cath.	Arterial thrombosis (vertebral artery)
19	6	7	M	Ductus arteriosus apertus	AA cath. + repeated aortography	A few hours after second aortography	Cerebral and renal contrast embolism
20	6	18	M	Intestinal carcinoid	RH cath. + angioc.	Unconscious after angioc.	Anesthetic complication
21	(7)	27		Cor pulmonale	RH cath.	6 days after cath.	Serious general condition
22	9	<1		A.S.D.	RH cath.	During cath.	Heart failure
23	(10)	<1		Infantile aortic coarctation	RH cath.	5 hr. after cath.	Heart failure (transient attack of ventricular fibrillation during cath.)

For key to abbreviations, see Table I.
*Hospital number is given in parentheses.

In 3 cases (1,2, and 17 in Table II) cardiac standstill occurred when, during ordinary venous or right heart catheterization, the catheter tip was situated in the right atrium, the right ventricle, and the superior vena cava,[13] respectively. These 3 patients were not regarded as seriously ill before the examination, but one of them (No. 2) was found at autopsy to have a fresh myocardial infarction. In Case 7, ventricular tachycardia appeared during right heart catheterization, could not be arrested, and within 24 hours proved fatal.[20] Case 22 died in heart failure during right heart catheterization. The latter 2 cases represented seriously ill patients where heart catheterization was performed on vital indication.

In 2 cases (11 and 14) the fatal outcome occurred during the induction of general anesthesia, after the catheter had been placed. They are regarded as being mainly anesthetic complications. In Case 12 cardiac standstill occurred when the catheter was introduced into the right ventricle under general anesthesia; this case is regarded as a combination of anesthesia and catheterization complications. In another case (No. 20), the patient was given short-acting barbiturate intravenously before angiocardiography but did not regain consciousness afterward. This patient had an intestinal carcinoid with unknown large spread to the liver[4]; presumably a large incretion of serotonin occurred during the examination and, since serotonin potentiates the action of barbiturates, the fatal outcome was regarded as a special variant of anesthetic complication.

In Case 13 cardiac standstill occurred when a catheter, which was not radioopaque, was introduced into the aortic arch prior to an intended thoracic aortography. In Case 18 a catheter was inadvertently advanced into the vertebral artery instead of the aortic arch; vertebral thrombosis with cerebellar necrosis followed with a fatal outcome.

Two cases of thoracic aortography (16 and 19) had a fatal outcome. Repeated contrast injections were made in both cases, in the one case with a few days' interval, in the other case with a few hours' interval. The first patient acquired reversible total anuria, which was successfully treated, but died several days after the examination from septic thrombo-embolism. The second patient died a few hours after the second contrast injection and showed signs of cerebral and renal contrast embolization.[20]

Seven cases of fatal complications arising out of completed angiocardiography were reported (4, 5, 8, 9, 10, 15, and 20). In 2 of these cases anesthetic complications were judged to be partly responsible; in 1 case air embolization from the contrast syringe was suspected.

The special techniques of direct needle puncture of the heart cavities and large vessels have not been analyzed in detail in this report. In 1 of our 12 hospitals, the left atrium is punctured with a paravertebral approach for pressure measurements or contrast injections; experiences from this method have been published elsewhere.[1] In a series of 167 patients (having mitral or aortic valvular disease) left atrial puncture was performed, and in 39 of them contrast injection under general anesthesia was made also. One fatal complication (cardiac tamponade and ventricular fibrillation) was reported, as well as 13 cases of major complications without fatal outcome (complications due mostly to angiocardiographies—cardiac tamponade, transient ventricular fibrillation, transient cardiac

standstill, etc.). In another of our hospitals, puncture of the left atrium is performed via the suprasternal route for pressure measurements.[32] Up to 1956, a total number of 197 such punctures were performed with 1 fatal complication (late, continued bleeding with cardiac tamponade, clinically undetected in a patient receiving anticoagulant treatment for suspected lung infarction).

In conclusion, two important facts should again be stressed. First, these advanced examinations were made mostly in seriously ill patients, often on vital indications preoperatively. Several cases have been reported where the patient died in his primary disease a few days or a few hours before a planned catheterization procedure. Secondly, the fatal complications occurred mostly in the first few years when these examinations were introduced, before the technique was fully elaborated, and before the present experience of indications, contraindications, and necessary preventive measures had been acquired. The figures for complications which are reported here are therefore not regarded to be representative of present-day conditions.

Transient Complications.—A survey of transient complications during or after right heart catheterization is given in Table III. In 2 patients transient ventricular fibrillation was observed during catheterization. One of them was a male surgical patient, showing no signs of heart disease, who did not show any

TABLE III. TRANSIENT COMPLICATIONS TO RIGHT HEART CATHETERIZATIONS, AORTIC-ARCH CATHETERIZATIONS AND ANGIOCARDIOGRAPHIES

Hospital number	1	2	3	4	5	6	8	9	10	1-12
Ventricular fibrillation							1	1		2
Ventricular tachycardia				4			1	2	1	8
Auricular tachycardia		2	1	2					2	7
Flutter, auricular fibrillation	8				2	2	1			13
Syncope		1			3		1		1	6
Right bundle branch block	10			6				2		18
Total A-V block				4		1				5
Intravasal cath. knot		3		2	1					6
Endomyocardial damage					5	1				6
Severe arterial spasm				1						1
Heart failure	2	2				1		2	5	12
Heart wall perforation					1					1
Arterial embolization									1	1
Severe fever reaction						1		1		2
Severe thrombophlebitis						1	1		1	3
Lung infarction							4			4

apparent sequelae afterward.[11] The other was a seriously ill infant with aortic coarctation (Case 23, Table II) who died 5 hours after the catheterization, probably from the primary disease. Other complications were ventricular tachycardia, flutter, and auricular fibrillation, syncope, right bundle branch block and total A-V block. In 6 cases the catheter tip formed a knot which could not be undone during the catheterization procedure. The catheter was then either extracted under general anesthesia or withdrawn as far as possible, to the main arm or leg vein, and removed by venotomy. This procedure did not cause remaining sequelae. A few cases of endomyocardial damage[3] and 1 case of severe arterial spasm after aortic catheterization were observed. In 4 cases of angiocardiography, with the catheter tip placed in the right ventricle, some contrast was deposited in the heart wall, and in 1 case even in lung tissue near the heart, but no late sequelae were observed. In several cases of advanced heart disease, acute heart failure occurred during catheterization. There was 1 case of arterial embolization during catheterization. Three cases of severe thrombophlebitis, with or without hematoma, were noted, and 2 cases of marked fever reaction. Other infections, e.g., inoculation hepatitis, were not reported. In 4 cases roentgenologic signs of small lung infarctions without remarkable clinical signs appeared during the first few days after catheterization; these were in a series of patients where repeated chest roentgenograms were taken routinely after catheterization.

It is probable that the given figures for transient complications are minimum ones. The frequency of demonstration of certain types of complications, e.g., small lung infarctions, depends on how extensively the patients have been examined during or after the catheterization procedure; some complications may have passed without clinical signs.

When a catheter is advanced via the right atrium and ventricle into the main pulmonary artery, especially when the catheter tip is in the outflow tract of the right ventricle, extrasystoles usually appear transiently. This has not been regarded as a complication. Similarly, a slight fever reaction or a localized thrombophlebitis in the vein used for introduction of the catheter has not been noted in Table III.

The special procedures of arterial puncture with introduction of a polyethylene catheter,[2] renal-vein catheterization by a similar technique (Hospital No. 8), liver-vein catheterization, or the use of a balloon near the catheter tip (for occlusion of a branch of the pulmonary artery or of an atrial septal defect) have not caused remarkable complications.

Sterility.—In several hospitals short-lasting pyrogenic reactions during or after catheterization appeared periodically. They have been explained as being due to the presence of pyrogenic substances in infusion solutions or in catheters. In most of our hospitals the catheters are kept in detergent solutions but are not sterilized by cooking, since this latter procedure is judged to make the catheters stiff and unduly breakable. Sterilization of instruments is otherwise performed according to the regulations of the Swedish Royal Medical Board (No. 24/1953), by cooking for 10 minutes or by a similarly effective method of heating. In a few of our hospitals, cooking of cardiac catheters is performed; polyethylene catheters are used only once.

Indications and Contraindications.—It is not possible to define detailed indications for right heart catheterization or angiocardiography. The indications vary according to the individual case, possibilities for operative treatment, the technical possibilities in the respective hospital, and the experience and scientific interests of the examining physician. It is equally difficult to define detailed contraindications; they are mostly relative in relation to the strength of the indications. In many cases, mostly children with congenital heart disease, examinations have been performed on vital indication (question of operability) in spite of the serious general condition of the patients. It is agreed that an acute inflammatory or degenerative myocardial process usually is a strong or absolute contraindication. Arrhythmias such as frequent extrasystoles or auricular fibrillation are regarded only as relative contraindications. The indications to discontinue a started catheterization procedure are also relative to the initial indications to perform the examination. Frequent auricular or ventricular extrasystoles usually call for a change in position of the catheter or a discontinuation. Slight discomfort in the patient seems to be relatively usual but serious discomfort or syncope are rare. Precordial pain is rare but calls for discontinuation.

Examinations Before Catheterization.—The extent and type of examinations which are made prior to catheterization depend largely on the type of case and the type of catheterization procedure which is going to be used. In addition to a careful case history and physical examination, heart-lung roentgenogram and electrocardiogram are always taken. Among the laboratory examinations which are made, varying in extent in the different hospitals, are these: prothrombin index, repeated blood cultures, nonprotein nitrogen, Wassermann's reaction, antistreptolysin activity, blood group determination, basal metabolic rate, blood volume determination, work tests for determination of the physical working capacity and the electrocardiographic work reaction, spirometry, phonocardiography, and electrokymography. Before aortography, and usually also before other contrast injections, renal function is always assessed by analyses of blood and urine and usually also by clearance determinations.

Medications.—When necessary, the patient should be optimally digitalized before the catheterization. Usually short-acting barbiturates are given orally an hour before catheterization; sometimes quinidine is given also. Before angiocardiography, morphine-scopolamine is given in the usual preoperative dosage, as well as an antihistaminic to prevent a hyperergic reaction to the contrast (a small initial test dose of contrast also is given before the main injection). Children are often given morphine-scopolamine (sometimes also atropine) instead of barbiturate before ordinary catheterization; in patients with respiratory insufficiency, too, barbiturates are considered unsuitable because of the tendency to cause respiratory depression. Penicillin is usually given for several days after the catheterization. During catheterization, a heparinized saline solution (producing a local but not a general effect) is mostly given continuously through the catheter to prevent clotting, and sometimes also procaine to prevent arrhythmia. A definite preventive effect of quinidine or procaine in this situation is, however, not judged to be proved.

After catheterization, analgesics and sometimes spasmolytics are indicated. Heparin is usually not used if definite local thrombophlebitis appears. Early mobilization after the procedure is probably useful to prevent local thrombosis, especially when a leg vein has been used. After angiocardiography, renal function should be controlled (diuresis, nonprotein nitrogen in blood, etc.). If angiocardiography must be repeated, an interval of at least 1 week is recommended.

Fluoroscopy, Catheterization Procedure.—The exposure to fluoroscopy should be kept as short as possible, both in regard to the patient and to the examiners. It is usually agreed that, with the smallest possible fluoroscopic field and at say 70 HkV. and 2 mA., the time of exposure should not exceed 20 minutes, or at the most 30 minutes. The examiner's hands are usually more exposed in the examination of children than of adults. The radiation doses were measured in one of our hospitals.[22] The doses probably vary considerably, according to the technique of catheterization and to the extent of preventive measures. The examiners may be exposed to 1.5 to 6 mr./min. (arm and legs) and less than 0.2 mr./min. (body and neck), respectively, while the patient's chest is considerably more exposed (1 to 8 r./min). An examiner therefore may be exposed up to or above 100 mr. per examination, and the number of examinations per examiner per week may in such cases have to be limited to 2 or 3 if an upper exposure limit of 300 mr./week is accepted.[40,41]

If the catheter is advanced so as to occlude a minor branch of the pulmonary artery in order to obtain the PCV (PC or wedge) pressure reflecting left atrial pressure, the risk of producing a lung infarction must be considered. Small infarcts probably may occur, judging from observed roentgenologic changes (Table III). The catheter is not allowed to remain in the wedged position more than 15 minutes, and not more than 5 or 10 minutes in some hospitals. In cases of pulmonary hypertension the time limit should probably be shorter.

The optimal size and stiffness of the catheter has been considered. For technical reasons, a moderately soft catheter of a relatively large diameter is advantageous, especially for blood sampling and also for angiocardiography where the largest possible catheter is needed. A double-lumen catheter is slightly more difficult to introduce into the pulmonary artery but is of great technical advantage in many cases. The slender catheters form intravasal or intracardiac knots more easily; the stiff catheters break more easily, hence may cause difficulties when they are to be extracted, and probably are more liable to cause mechanical damage.

General Considerations.—The performance of heart catheterizations, angiocardiographies and similar examinations should be concentrated in the large hospitals where a diagnostic unit with experienced examiners and good technical equipment can be organized, and where are present also those other special units which are needed for collaboration and for full use of the special information obtained by the diagnostic procedures. It is agreed that between 50 and 100 catheterizations per year are the minimal number which allows the diagnostic unit to retain a high technical standard. For angiocardiographies, a similar or slightly lower figure is probable.

A good contact between patient and examiner is important for successfully carrying out a complete examination. In some of our hospitals this comes naturally since the examination is made by the physician who is clinically responsible for the patient. In other hospitals this is not possible, and the examination is performed by other physicians (clinicians or clinical physiologists); the necessary contact can be obtained then by special ward rounds, preliminary examinations, and conferences. A few of us, however, believe this to be an unsuitable procedure.

It is generally agreed that at least two medical examiners should take part in a catheterization in order to maintain a high technical standard and as a preparation against complications, even when it is possible for one examiner to perform the simpler procedures with only technical assistance. At angiocardiographies one of the examiners is a roentgenologist; in addition, an anesthetist is needed. The anesthetist should be one who has specialized in the procedure. Besides the two medical examiners, at least three nurses and technical assistants are needed, often more.

The catheterization room should be at least 30 to 40 M.^{2} in size. It is preferable to arrange the equipment for angiocardiography in the catheterization room or in a neighboring room.

The maximum number of catheterizations that an examiner can perform per week depends on several factors, including how differentiated one examination is and how long it lasts. For several reasons, including psychologic ones, it is believed that this activity should be combined with other duties where the risk of radiation is absent. This is the case in all our hospitals; one to four examinations per week is the usual range.

Examination of children is considered to require special pediatric experience. On the other hand, in some of our hospitals, pediatric specialists also catheterize adult patients.

It is not judged to be allowable to catheterize patients who are not under hospital care. About half of us are of the opinion that heart catheterization on volunteers for scientific purposes is permissible, while the rest do not agree.

Preparatory Measures Against Complications.—The most important measure against complications is to have an experienced, well-organized, and well-equipped team for the examinations. The team must possess good experience in all diagnostic and therapeutic measures against possible complications (e.g., arrhythmia, heart failure, pulmonary edema, shock, circulatory standstill). The examiners and the technical personnel should be trained to meet emergency situations; necessary instruments and drugs should be easily accessible.[15,37] Continuous recording or display of the patient's electrocardiogram or arterial blood pressure is regarded as necessary.

DISCUSSION

Catheterization of heart and large vessels as a diagnostic method, with or without angiocardiography, is now generally accepted as an indispensable tool in certain diseases, usually for preoperative evaluation. This is so in spite of the serious complications which may rarely occur. The risk of complications, how-

ever, demands (1) a strict evaluation of indications and contraindications, and (2) a high technical standard in the procedure. When these demands are met, it is believed that the present-day risk of complications is smaller than reported above.

The rate of fatal and nonfatal complications in right heart catheterization and angiocardiography was reviewed earlier[7,9,24,36] and several individually fatal[10,30] or nonfatal[5,8,11,12,19,20-22,25-27,29,31,33-35,39] cases reported in the literature. The technique in, and indications and contraindications for, such procedures were also extensively described.[1,2,6,7,14,16-18,20,21,24,25,32,33] The risk of fatal complications due to right heart catheterization, as reported here, seems to be about twice as high as the risk of fatal circulatory standstill in general anesthesia[28] or about two to four times as high as the risk of fatal complications in blood transfusions.[38] The risk of fatal complications arising out of angiocardiography and especially thoracic aortography seems to be considerably higher.

SUMMARY

Experiences from 12 Swedish hospitals concerning catheterization of the heart and large vessels, with or without contrast injection, have been reviewed with respect to rate of fatal and nonfatal complications, indications and contraindications, technique, and preventive measures. The rate of certain fatal complications due to right heart catheterization was 5/5,859; to completed or incomplete angiocardiography 9/2,451; and to completed or incomplete thoracic aortography 5/340.

REFERENCES

1. Bagger, M., Björk, V. O., and Malmström, G.: Am. Heart J. **53**:91, 1957.
2. Bernéus, B., Carlsten, A., Holmgren, A., and Seldinger, S. I.: Scandinav. J. Clin. & Lab. Invest. **6**:217, 1954.
3. Biörck, G., and Krook, H.: Acta cardiol. **6**:101, 1951.
4. Biörck, G., Axén, O., and Thorson, Å.: Am. Heart J. **44**:143, 1952.
5. Biörck, G., Sylwan, T., and Lindblom-Tillman, G.: Acta cardiol. **5**:509, 1950.
6. Brodén, B., Hanson, H. E., and Karnell, J.: Acta radiol. **29**:181, 1948.
7. Cournand, A., et al.: Circulation **8**:769, 1953.
8. Crawford, E. S., et al.: Surg., Gynec. & Obst. **2**:129, 1957.
9. Dotter, C. T., and Jackson, F. S.: Radiology **54**:527, 1950.
10. Goodwin, J. F.: Brit. Heart J. **15**:330, 1953.
11. Gordh, T., Linderholm, H., and Ström, G.: Anesthesiology **17**:358, 1956.
12. Gyllenswärd, A., et al.: Nord. med. **53**:317, 1955.
13. Haeger, K., Juhlin, I., and Krook, H.: Am. Heart J. **50**:471, 1955.
14. Holling, H. E., and Sak, G. A.: Brit. Heart J. **12**:153, 1950.
15. Hosler, R. M.: Cardiac Resuscitation, Springfield, Ill., 1954, Charles C Thomas.
16. Jönsson, G.: Acta radiol. **29**:536, 1948.
17. Jönsson, G., Brodén, B., Karnell, J.: Acta radiol. **32**:486, 1949.
18. Jönsson, G., Brodén, B., Karnell, J.: Acta radiol. Suppl. **89**, 1951.
19. Kirstein, L., et al.: Acta radiol. **47**:169, 1957.
20. Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B.: Diagnosis of Congenital Heart Disease, Chicago, 1955, Year Book Publishers, Inc.
21. Krčlilek, A., Krčilková, M., and Skop, V.: Abstract, Second European Congress of Cardiology, Stockholm, 1956, p. 151.
22. Landtman, B.: Acta paediat. **39**:1, 1950.
23. Larsson, L. E.: Acta radiol. **46**:680, 1956.
24. Lenègre, J., Coelho, E., Kjellberg, S. R., Landtman, B., Snellen, H. A., Ström, G., Tybjaerg-Hansen, A., and Wood, P.: Round Table Conference, Second European Congress of Cardiology, Stockholm, 1956.

25. Levi, V., Actis-Dato, A., and Angelino, P. F.: Abstract, Second European Congress of Cardiology, Stockholm, 1956, p. 162.
26. Mannheimer, E., Landtman, B., and Melin, K. A.: Cardiologia **19**:337, 1951.
27. McMichael, J., and Mounsey, J. P. D.: Brit. Heart J. **13**:397, 1950.
28. Milstein, B. B.: Ann. Roy. Coll. Surgeons England **19**:69, 1956.
29. Morato-Portell, J.Ma, et al.: Abstract, Second European Congress of Cardiology, Stockholm, 1956, p. 183.
30. Nightinggale, J. A., and Williams, B. L.: Brit. Heart J. **17**:113, 1955.
31. Padovcova, H., and Bor, I.: Abstract, Second European Congress of Cardiology, Stockholm, 1956, p. 202.
32. Radner, S.: Acta med. scandinav. **151**:223, 1955.
33. Scebat, L., Renais, J., and Meevs-Bithe, L.: Abstract, Second European Congress of Cardiology, Stockholm, 1956, p. 222.
34. Stern, T. N., et al.: AM. HEART J. **44**:448, 1952.
35. Strano, A., Filocamo, G., and Saponaro, A.: Abstract, Second European Congress of Cardiology, Stockholm, 1956, p. 245.
36. Warburg, E.: Acta med. scandinav. **151**:209, 1955.
37. Wegria, R., et al.: Circulation **8**:1, 1953.
38. Winer, A. S., et al.: J.A.M.A. **151**:1435, 1953.
39. Zimdahl, W. T.: AM. HEART J. **41**:204, 1951.
40. Recommendations of the International Commission on Radiological Protection: Brit. J. Radiol. (Suppl. 6) 1955.
41. Editorial: Lancet **2**:467, 1957.

Clinical Reports

PERIPHERAL A-V FISTULA OF FIFTY-SEVEN YEARS' DURATION WITH REFRACTORY HEART FAILURE

EDWARD R. DORNEY, M.D.*

ATLANTA, GA.

THE purpose of this presentation is to reaffirm peripheral A-V fistula as a cause of congestive heart failure in the otherwise normal heart and to enter into the literature a case of traumatic peripheral A-V fistula of 57 years' duration.

CASE REPORT

G. E., a 68-year-old white man, was admitted to the Emory University Hospital for treatment of refractory heart failure. He was a retired railroad worker who stated that he had always been in excellent health. At approximately the age of 10 years, he sustained a .32 caliber pistol shot wound in the left thigh. The bullet entered the medial aspect of the thigh above the knee. The point of exit was in the lateral aspect of the thigh superior to the entrance wound. The bone was damaged. He recalls having been told that the bullet had penetrated the blood vessels of his leg. He stated that, since the time of the accident, there had been a "cat crying" in his leg, and the left leg had been larger than the right but had caused him no appreciable difficulty. It had been necessary for him to wear an elastic stocking on his leg to prevent swelling. During his active life, he had been engaged in an occupation requiring heavy manual labor. He stated that he had noticed "racing" of his heart for short periods of time during the past 30 years. There was no shortness of breath or chest pain. Approximately 6 years before admission, he was seen by his physician during a bout of rapid heart rate, was given digitalis, and had been on maintenance dosage until the present time. Also, he had been placed on a low-sodium diet. He denied any shortness of breath or paroxysmal nocturnal dyspnea. He was doing well until approximately 6 weeks before admission, at which time he began to gain weight rapidly and was unable to lie flat in bed because of dyspnea. He visited his physician who gave him an injection of a mercurial. Diuresis followed with a loss of 10 pounds of weight within the next 24 hours. At the same time, he was begun on Diamox, 250 mg. each day. He rapidly regained weight, however, and during the next 2 to 3 weeks received 2 or 3 injections of mercurials, with diuresis following each injection. His last mercurial injection was 3 weeks prior to admission. This produced no diuresis. He stated that, beginning with the first mercurial injection, he had noticed constant nausea and dizziness which seemed to be worse on reclining. His family noticed that he had become progressively more swollen during the 2 weeks prior to admission, was unable to eat, and was becoming weak. The patient denied any symptoms suggestive of myocardial infarction, angina pectoris, or rheumatic heart disease in the past. He stated that he had hypertension for many years, but that more recently he was told that his blood pressure was not high.

Received for publication April 15, 1957.

*Associate in Medicine, Department of Medicine, Emory University, Atlanta, Ga.

Review of systems was negative with the exception of the genitourinary tract which showed 3 times nocturia for many years. The urinary stream was said to be diminished in caliber and force.

On physical examination, the temperature was 98.6°F., pulse 120, respirations 18, blood pressure 140/80 mm. Hg. The patient was an elderly emaciated man who appeared chronically ill. His color was waxy and yellow. His eyes, ears, nose, and throat were within normal limits. His neck was supple. Neck veins were distended and were seen to pulsate irregularly. The chest showed increased A-P diameter. There were a few fine moist râles in both lung bases posteriorly. The heart was markedly enlarged to palpation. The apex impulse was diffuse and leftwardly displaced. No murmurs were heard at the base of the heart. Heart sounds varied in intensity from beat to beat, and there was a Grade 2 apical systolic murmur not associated with a thrill. There were multiple premature ventricular contractions noted to occur in bigeminy. The liver was enlarged 7 cm. beneath the right costal margin. The spleen was not palpable. Fluid was thought to be present within the abdomen. The lower portion of the aorta was dilated and pulsatile. The left external iliac artery could be palpated down to Poupart's ligament. Four plus sacral edema was present, and four plus peripheral edema extended from the knees downward. Peripheral pulses were not palpable in the lower legs. The left thigh was approximately 4 inches larger in diameter than the right thigh. There was a continuous machinery-like murmur audible along the course of the left femoral artery, and a thrill was palpable just superior to the entrance scar on the medial aspect of the thigh. There was a marked dilatation of the femoral artery in its proximal location, and a continuous murmur was heard over this area as well. The left leg was warmer than the right leg. No varicosities were identified. Entrance and exit bullet wound scars were identified on the medial and lateral aspects of the left thigh. The left leg was not longer than the right leg.

An electrocardiogram revealed no auricular activity. There were polyfocal premature ventricular contractions seeming to occur in bigeminy and in runs of ventricular tachycardia. The hemogram was well within normal limits. Urinalysis was normal. X-ray examination of the chest showed marked cardiomegaly with left pleural effusion and pulmonary congestion compatible with the clinical diagnosis of congestive heart failure. Weight at the time of admission was 181 pounds. The chest film made on admission is shown in Fig. 1. Electrolyte studies done at this time showed a CO_2 of 25.3 meq./L., plasma chlorides of 98.8 meq./L., sodium 33.6 meq./L., and potassium 4.2 meq./L. N.P.N. was 47 mg. per cent. The patient was placed at bed rest, given a 200 mg. low-sodium diet, and potassium 40 meq./L. each day by mouth. On this routine, the patient began to feel better. He was eating and sleeping well. The heart rhythm continued irregular, but there were longer runs of regular rhythm than had been present at the time of admission. The only disquieting note was the gradual, persistent gain in weight. For this reason, the patient was given Thiomerin, but despite the mercurial injection he continued to gain weight. The heart rhythm remained irregular, and the clinical condition was obviously deteriorating. The patient's weight rose to 186¼ pounds, and it was decided that immediate operation with closure of the A-V fistula would be necessary as a lifesaving procedure. On Dec. 22, 1955, an A-V fistula of the left thigh was excised under spinal anesthesia by Dr. F. W. Cooper, Jr. The patient tolerated the procedure well, and it was his own observation that shortly after the closure of the A-V fistula the forceful beating of his heart was no longer evident. The patient was returned to his room in good condition. Several hours after the operation, it was noted that the premature ventricular contractions were coming at 3 to 4 per minute, whereas, previous to the operation, they had occurred as bigeminy with short runs of ventricular tachycardia. Diuresis began almost immediately postoperatively, and continued during the remainder of his hospital stay. At the time of discharge on Jan. 10, 1956, the patient's weight was 134¾ pounds (a loss of 47 pounds since operation). Following the operation, he was maintained on a 200 mg. low-sodium diet, and quinidine sulfate 0.2 Gm. every 6 hours. No diuretics or digitalis were given. Postoperative convalescence was unremarkable except for a hematoma at the operative site which was caused by the use of heparin 2 to 3 days postoperatively. It was felt that, due to the long duration of this man's heart disease, he should be digitalized before returning home. This was carried out slowly 2 days before discharge. After discharge, the patient did well. Consultation with his physician revealed the recurrence of the premature ventricular contractions. Shortly after dis-

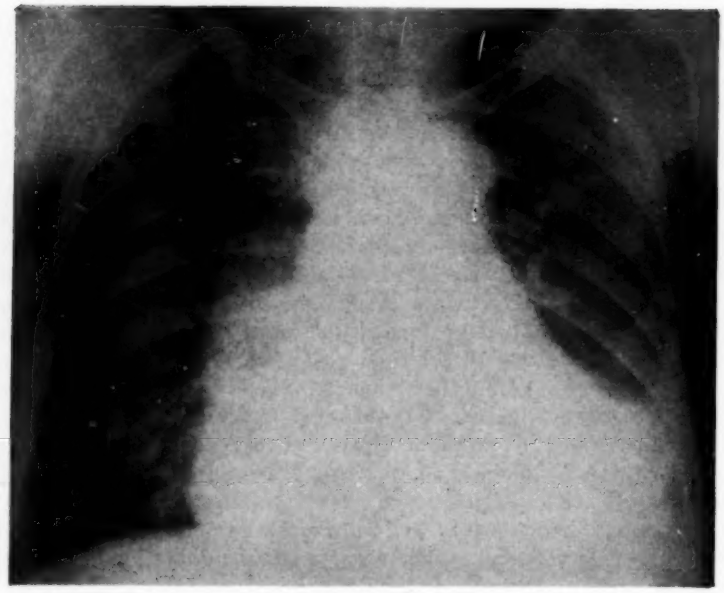


Fig. 1.—Posteroanterior film made at time of admission.

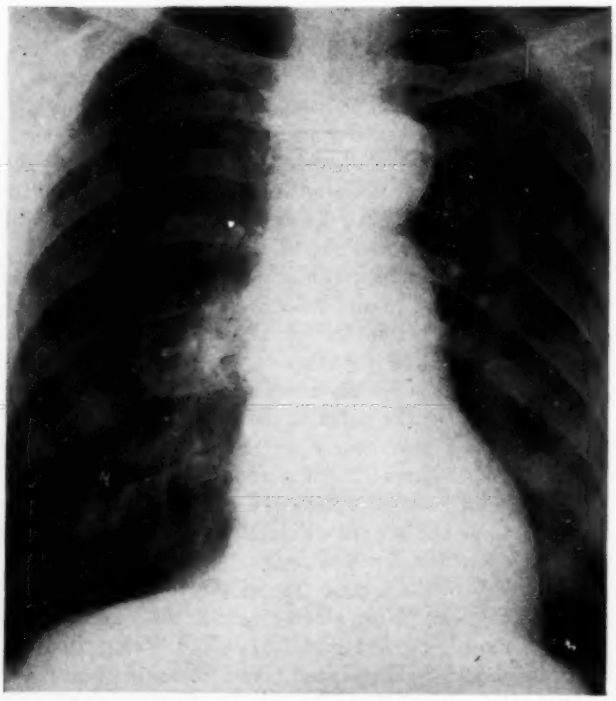


Fig. 2.—Chest film 3 months after operation.

charge, digitalis was again discontinued and has not been reinstituted. Sodium restriction was discontinued approximately 1 month after discharge, and the patient has received no cardiotonic drugs nor other therapy directed toward the heart since that time. At the present time, approximately 1 year later, he is completely ambulatory, has no signs of congestive failure, and is carrying on normal daily activities with no difficulty. The heart size has decreased as shown in Fig. 2.

DISCUSSION

It is a well-accepted fact that peripheral A-V fistula may be a cause of congestive heart failure.[1] The speed of development of the failure is a function of the size of the fistula and the condition of the heart at the time of creation of the fistulous tract.

In this patient with a normal heart, congestive failure developed 57 years after establishment of the fistula. Once failure was apparent, it was not amenable to the usual means of therapy but responded dramatically to surgical removal of the fistulous connection.

It would seem prudent, therefore, in all cases of refractory heart failure, to examine the past history carefully for the possibility of a peripheral A-V fistula. Auscultation and palpation should be carried out over all scars, traumatic and surgical, in search of the characteristic bruit and thrill. The presence of the suspected fistula can be confirmed by: (1) slowing of the pulse with manual compression of the fistula (Branham's sign) and (2) demonstration of an elevated oxygen content in the blood of the involved vein.

REFERENCE

1. Warren, J. V., Nickerson, John L., and Elkin, D. C.: J. Clin. Invest. **30**:210, 1955.

ELECTROCARDIOGRAPHIC CHANGES RESEMBLING MYOCARDIAL INFARCTION IN A YOUNG CHILD

JAMES E. DOHERTY, M.D., AND KATHARINE DODD, M.D.

LITTLE ROCK, ARK.

AS NEARLY as we have been able to ascertain, the occurrence of electrocardiographic findings resembling myocardial infarction in a previously healthy young child is rarely reported in the literature. It is the purpose of this report to record such an instance in a child who recovered.

CASE REPORT

M. C., a white girl, 4 years and 9 months old, was admitted to the University of Arkansas Hospital, Dec. 2, 1952. Two weeks prior to the present illness, she had coryza and moderate fever. Two days before admission, fever, abdominal cramps, and pain in the leg muscles were noted. The child had had frequent colds in the past, but no history of rheumatic fever, by name or symptom, or of any other serious illness was obtained. In the emergency room, the patient had a generalized convulsion. The child's temperature was 100° F. rectally, pulse rate 180 per minute, respirations 28, blood pressure 80/70 mm. Hg. Except for weakness of the legs and absence of reflexes, probably sequelae of the previous convulsion, findings were limited to the heart. The point of maximum impulse was within the mid-clavicular line in the fifth left intercostal space. A marked sinus tachycardia (180 per minute) and a systolic gallop were present. No murmurs or rubs were heard. There was moderate right upper quadrant tenderness in the region of the liver.

Laboratory Data.—Smears and cultures of the throat for diphtheria were negative. Urinalysis was negative except for a slightly positive test for acetone. Hemogram: hemoglobin 12 Gm. per 100 c.c.; red blood count 3.6 million per cubic ml.; white blood count 15,500 per cubic ml., differential: 2 juveniles, 5 bands, 53 polymorphonuclear leukocytes, and 40 lymphocytes. Serologic test for syphilis was negative. Corrected sedimentation rate on Dec. 4, 1952, was 52 mm. per hour. Spinal fluid on Dec. 2, 1952: pressure not recorded; one cell per cubic ml.; protein 33 mg. per 100 ml.; sugar 63 mg. per 100 ml. Tuberculin and histoplasmin skin tests were negative. Roentgenogram of the chest on the day of admission was unsatisfactory; however, one performed on Dec. 5, 1952, revealed generalized cardiac enlargement (Fig. 4,*A*). An electrocardiogram obtained on the day of admission revealed a rate of 130 (sinus tachycardia); P-R interval 0.13 second, QRS 0.09 second, QT 0.28 second. The trace is reproduced in Fig. 1 and reveals extreme S-T deviation with a Q wave of significant duration (0.04 second) in Leads aV_L and V_3. A rare premature contraction of ventricular origin is noted.

Course in Hospital and Follow-Up.—At the time of admission, the patient was put to bed, digitalized, and started on oxygen therapy. Penicillin was given for the first 2 weeks and digitalis continued for nearly a month. During this period the patient's temperature was normal except for 2 days, 4 weeks after her admission, when it rose to 104° F. The episode was thought to be an acute laryngotracheitis. She was discharged from the hospital on Jan. 6, 1953, markedly improved. She returned on several occasions, the last time on Feb. 29, 1956 more than 3 years after her original illness, and was clinically well at each visit.

From the Departments of Medicine and Pediatrics, University of Arkansas Medical Center, Little Rock, Ark.

Received for publication April 18, 1957.

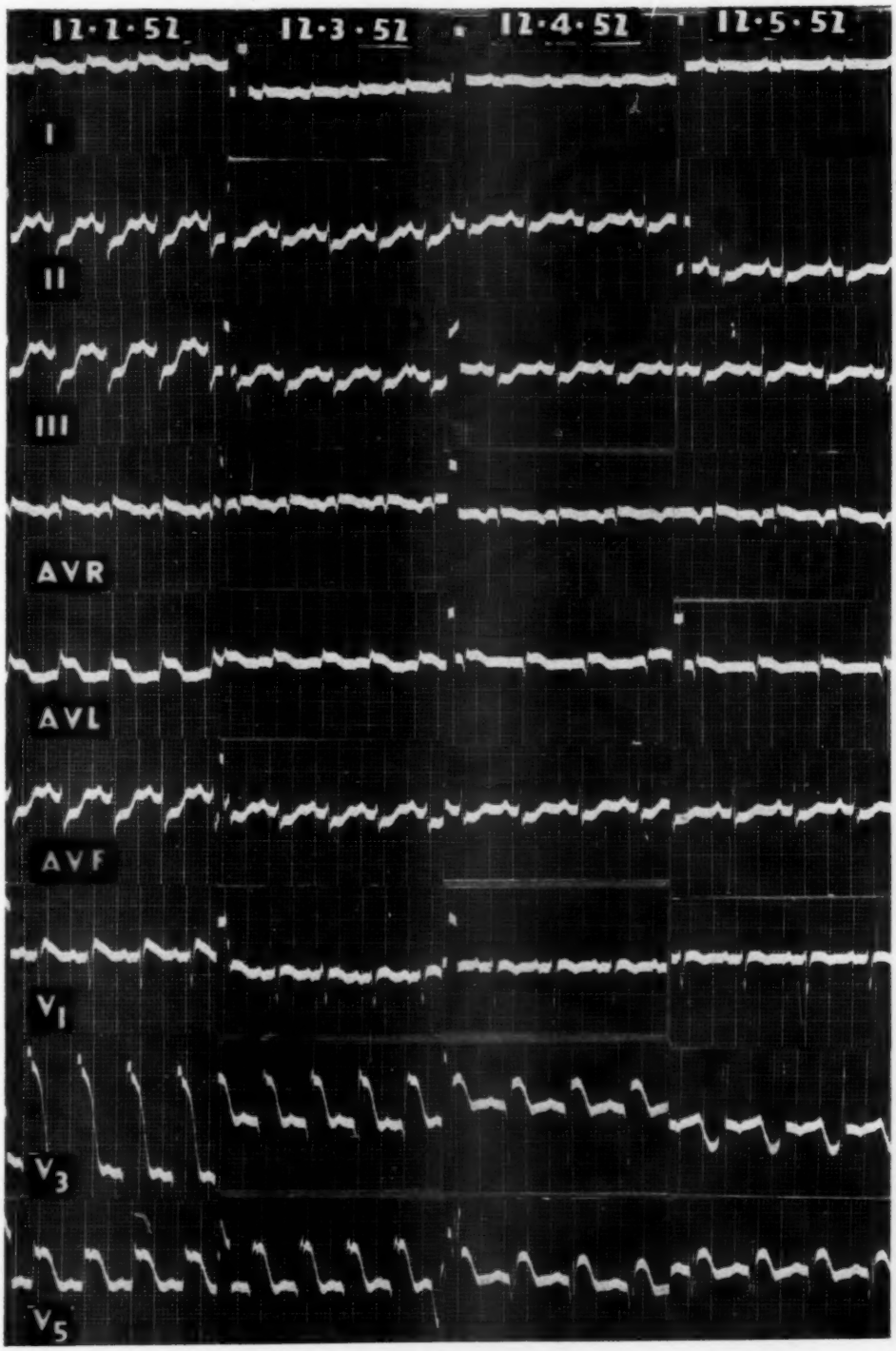


Fig. 1.—Electrocardiograms Dec. 2, 1952, Dec. 3, 1952, Dec. 4, 1952, and Dec. 5, 1952. This series illustrates the marked S-T and T-wave changes with the development of Q waves of abnormal duration during the early course of hospitalization. These changes are those usually seen in acute anterolateral myocardial infarction. (V_3, 12-2-52, mounted upside down.)

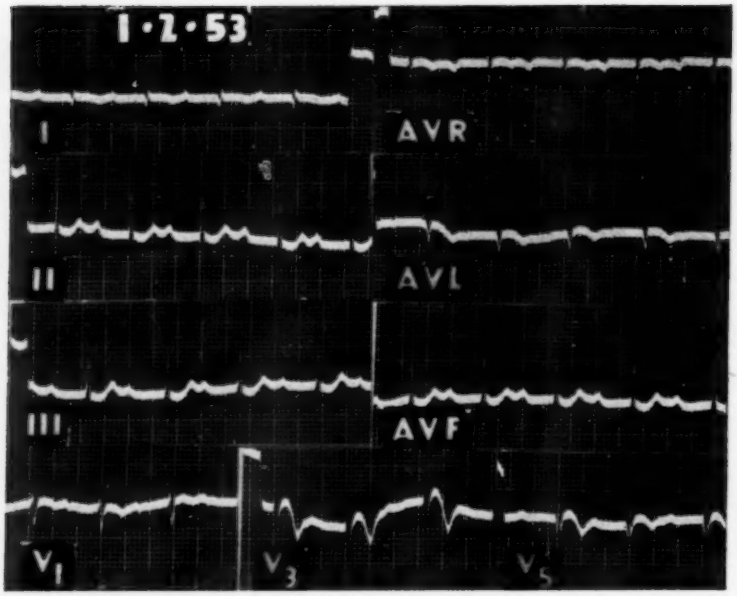


Fig. 2.—Electrocardiogram Jan. 2, 1953. This electrocardiogram demonstrates P-R prolongation to 0.30 second and minimal S-T changes. Q waves of abnormal duration persist in Leads I, aV_L, V_5, and V_6. A small R wave now precedes the wide deep S wave in Lead V_3. These findings were felt to be compatible with continuing evolution of an acute anterolateral myocardial infarction with superimposition of digitalis effects.

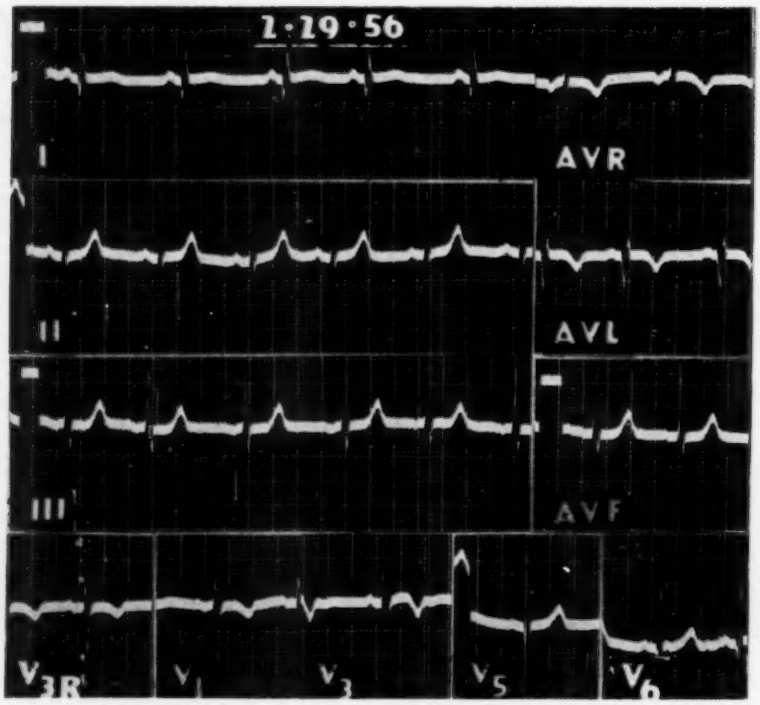
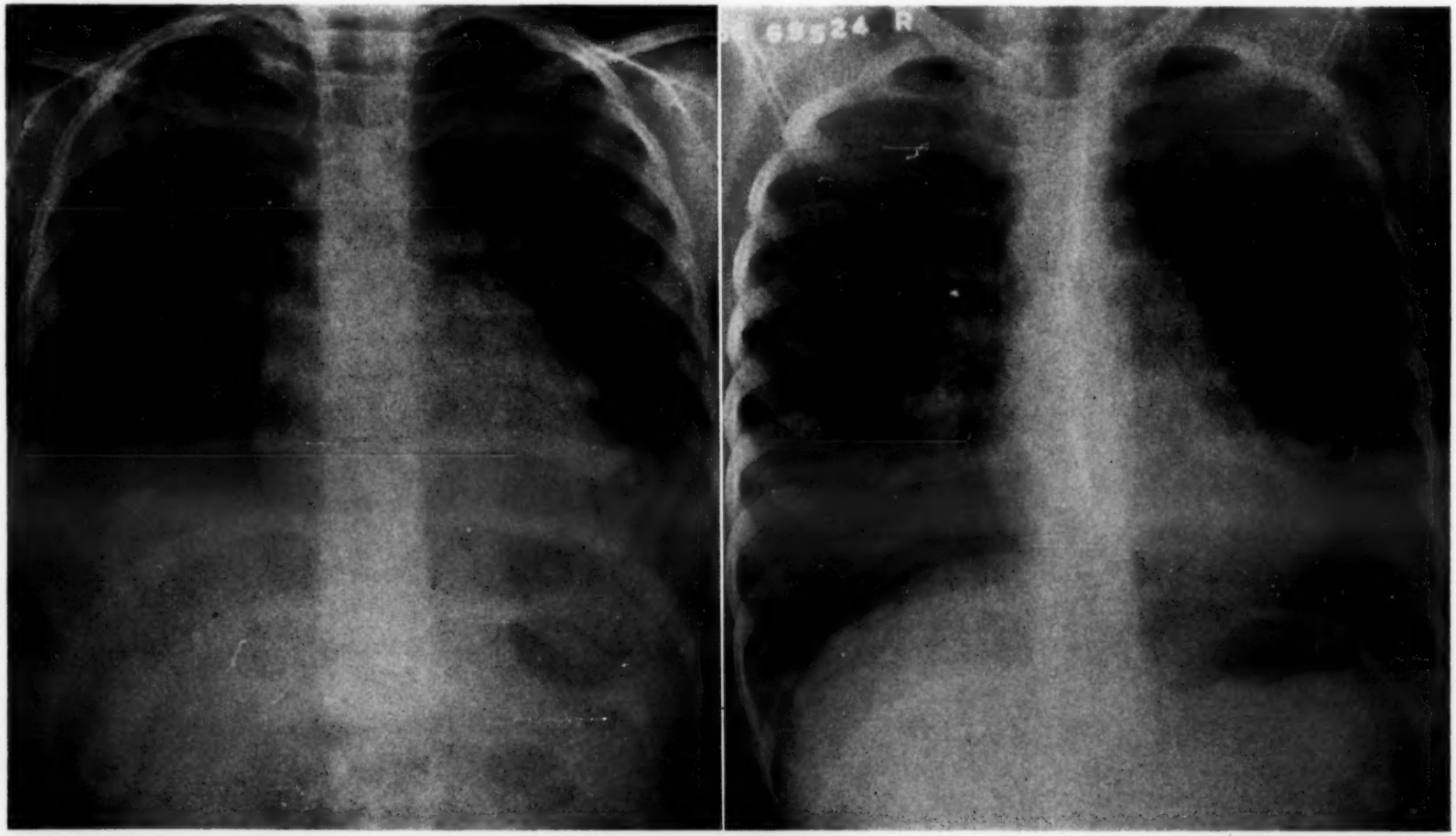
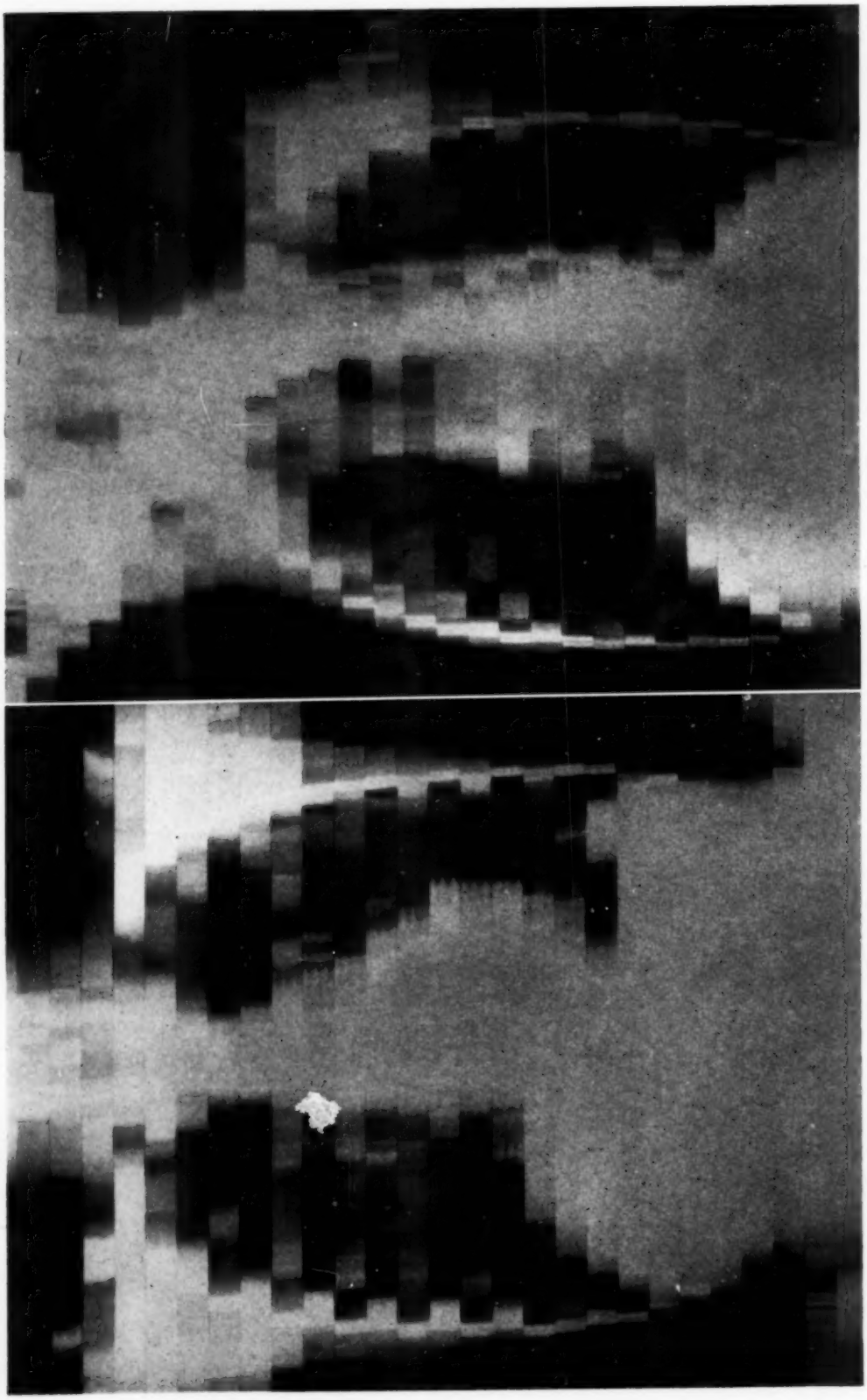


Fig. 3.—Electrocardiogram Feb. 29, 1956. Q waves with a duration of 0.04 second are present in Leads I and aV_L. Q waves in the precordial leads are now of normal duration.



A. *B.*

Fig. 4.—*A*, Posteroanterior x-ray of the chest Dec. 5, 1952. Cardiac enlargement is present. *B*, Posteroanterior x-ray of the chest Feb. 29, 1956. Abnormal cardiac contour is noted. An area of "inactivity" in the left anterior ventricular segment in the region of the bulge noted at the lower left cardiac border on this film was described at fluoroscopy.



B.

A.

Fig. 5.—Posteroanterior kymogram (*A*) and lateral kymogram (*B*) obtained May 9, 1956. An area of diminished activity at the left lower anterior border of the heart is noted.

Electrocardiograms.—Serial electrocardiographic traces obtained on Dec. 3, 4, and 5, 1952, are reproduced in Fig. 1 and reveal similar changes, with the Q waves previously described becoming more striking and S-T segment changes regressing. Traces obtained almost daily thereafter appeared to reveal typical evolutionary changes of myocardial infarction. The abnormal Q waves were observed on Jan. 2, 1953, in Leads I, aV_L, V_3, V_5, and V_6 in association with a prolonged P-R interval (Fig. 2). A trace obtained Feb. 29, 1956, revealed persistence of Q waves in Leads I and aV_L and a tendency for the Q waves in the precordial leads to disappear (Fig. 3).

Roentgenograms of the chest on Dec. 5, 1953, and Feb. 29, 1956, revealed some left ventricular enlargement (Fig. 4,*A* and *B*). During fluoroscopy at the time of the latter examination, peculiar pulsations rather high on the left ventricular border were noted. These were not thought to be paradoxical in nature. Fluoroscopy was repeated 3 years after the original illness, and kymograms were obtained in posteroanterior and lateral projections (Fig. 5,*A* and *B*). Pulsations were not altogether normal at the left ventricular border, but, again, paradoxical pulsations were not present. There was an area 3 cm. in length along the left anterior border of the heart which was definitely underactive compared to adjacent areas. The radiologist stated that these findings were consistent with an area of localized myocardial damage.

SUMMARY

The case report of a previously healthy 5-year-old white girl who, during a febrile illness, exhibited findings consistent with a diagnosis of myocardial infarction has been presented. Serial electrocardiograms over a period of 3 years demonstrate fairly typical evolutionary changes of a myocardial infarction. Roentgenographic and fluoroscopic findings seem to support this diagnosis.

VENTRICULAR SEPTAL DEFECT WITH AORTIC INCOMPETENCE SIMULATING PATENT DUCTUS ARTERIOSUS

J. Gordon Claypool, M.D., Wm. Ruth, M.D., and T. K. Lin, M.D.

Kansas City, Kans.

ROGER'S classic description of ventricular septal defect was published in 1879.[1] Ventricular septal defect with accompanying aortic insufficiency was first described in 1921, by Laubry and Pezzi.[2] From the available medical literature we were able to collect 36 cases of ventricular septal defect* with aortic insufficiency.[2-18] With the current possibility of surgical correction in cases of ventricular septal defect and other abnormalities, the differential diagnosis assumes marked importance, making the report of this case worth while.

The following case report presents the problem of diagnosis and subsequent course in a case of ventricular septal defect with aortic incompetence.

Table I. Catheterization Studies

Source of Blood Sample	O_2 Content Vol. %	O_2 Sat. %	Pressure (mm. Hg) S. D.	Pressure (mm. Hg) Mean	Physiologic Studies	
SVC	10.76	68.8			Oxygen capacity	15.98
IVC	12.76	81.7		3.5	Oxygen consumption	85 c.c. (cal.)
RA	10.78 9.04	68.9 57.7		1	S. F. (c.c./min.)	2,005
RV						
Inflow	13.28	85.1			P. F. (c.c./min.)	5,857
Mid	12.60	80.7	82/0-7	30	L-to-R Shunt (c.c./min.)	3,852
Outflow	12.41	79.5			C. I. (L./min./M.^{2})	3.04
PA	12.81 13.12	82.1 83.4	82/43	48	S. V. (c.c.)	13.3
FA	14.34	91.3	154/60	100	S. I. (c.c./M.^{2})	20.1

S.F. = systemic flow; P.F. = pulmonary flow; C.I. = cardiac index; S.V. = stroke volume; S.I. = stroke index.

From the Cardiovascular Section of the Department of Medicine, University of Kansas Medical Center, Kansas City, Kans.

Received for publication April 25, 1957.

*Including a few cases of Eisenmenger's complex.

CASE REPORT

The patient, P. S. R., a 5-year-old white girl, was admitted to Kansas University Medical Center on Feb. 17, 1956. Her history revealed that an imperforate anus had been discovered at birth and had been repaired immediately. At 1 month of age the patient's mother consulted a physician because of wheezing and was told that the child had heart trouble. Development progressed slowly, the child sitting at 2 years and talking at 2½ years.

By July, 1955, she tired easily and was anorexic. She was unable to keep pace with her class mates. She had no orthopnea, edema, or cyanosis.

Examination as an outpatient at the Kansas University Medical Center in November, 1955, revealed a loud, Grade 5 machinery-type murmur in the pulmonic area. Cardiac catheterization was deferred because of upper respiratory infection with fever. A tentative diagnosis of aortico-pulmonary communication and marked pulmonary hypertension, probably patent ductus arteriosus, was made.

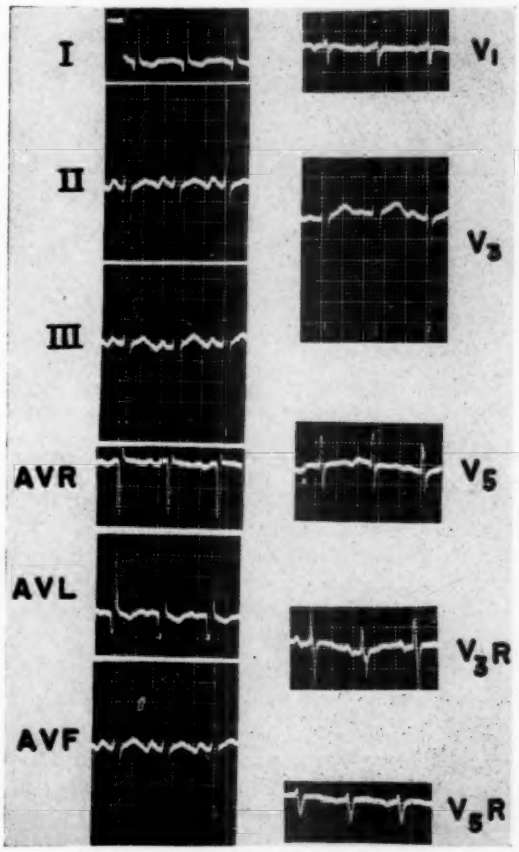


Fig. 1.—Admission ECG. Full standard was used for limb leads V_3R and V_5R. Half standard was used for the left chest leads.

In June, 1956, a thoracotomy was performed elsewhere to repair the patent ductus. A patent ductus was not found. The pericardium was not opened. The parents were informed of the failure to demonstrate the patent ductus and were advised to return the child to the University Hospital.

On admission, physical examination revealed a poorly-developed, poorly-nourished white girl, small for her age. The blood pressure in both arms was 130/40-0 mm. Hg; pulse 100, regular

and bounding; and temperature 98.2°F. There was no cyanosis or clubbing. Examination of the heart revealed a marked systolic thrill over the entire precordium, most marked in the second left intercostal space. The point of maximal impulse was in the sixth and seventh interspaces in the AAL. P_2 was greater than A_2. A Grade 5 machinery-type murmur was heard in the pulmonic area. A Grade 2 apical diastolic rumbling murmur was detected. The liver was down 2 cm. below the right costal margin. Collapsing femoral pulses were present.

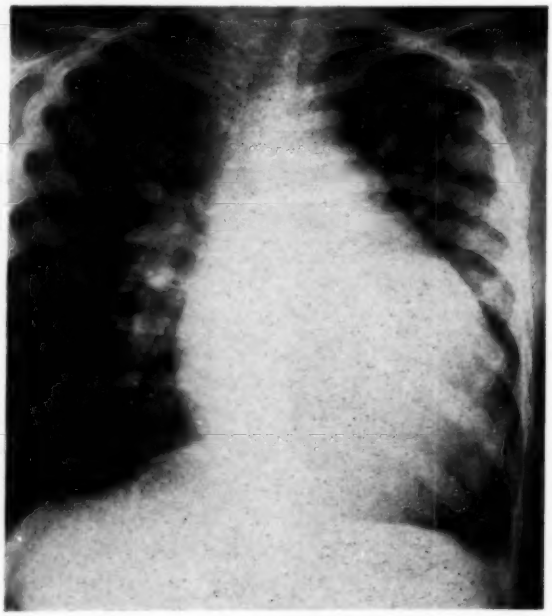


Fig. 2.—Posteroanterior view of the chest shows marked cardiac enlargement and markedly increased pulmonary vascular markings.

Pertinent laboratory data were as follows: hematocrit 43 c.c., hemoglobin 84 per cent, sedimentation rate Cutler 10 mm./hr., fasting blood sugar 92 mg. per cent, blood urea nitrogen 13.2 mg. per cent, negative serology. Rheumatic activity study was within normal limits. An ECG (Fig. 1) was interpreted as showing left ventricular hypertrophy and ischemia and possibly right ventricular hypertrophy. Chest x-ray demonstrated marked cardiac enlargement and increased pulmonary vascular markings (Fig. 2). The phonocardiogram (Fig. 3) showed distinct systolic and diastolic murmurs.

Hospital Course.—Temperature ranged from 99.4 to 102.4°F. Since she had been on digitalis, it was continued in the form of digitoxin 0.075 mg. daily, and procaine penicillin 600,000 units daily was started.

Cardiac catheterization (Table I) was done on Feb. 20, 1956, at which time severe pulmonary hypertension was confirmed (80/43 mm. Hg, mean 48 mm. Hg). An increase of 2.8 vol. per cent oxygen content from the right auricle to right ventricle indicated a large L-to-R shunt at the ventricular level. The femoral arterial oxygen saturation was 91.1 per cent which was considered to be the lower limit of normal in our laboratory for children under anesthesia (rectal Avertin). The femoral arterial pressure was 154/60 mm. Hg.

The diagnoses considered after catheterization were (1) ventricular septal defect with aortic septal defect, (2) ventricular septal defect with aortic regurgitation, (3) ruptured sinus of Valsalva into right ventricle with or without ventricular septal defect, and (4) aortic septal defect with marked pulmonary regurgitation.

On Feb. 25, 1956, a thoracotomy with hypothermia was done by Drs. C. Hardin and F. Kittle. The right ventricle was opened. A high ventricular septal defect was found and closed. The patient then had cardiac arrest. Cardiac massage with defibrillation and cardiac stimulants failed to restore normal sinus rhythm. Resuscitation was attempted for 1 hour, after which time the patient was pronounced dead.

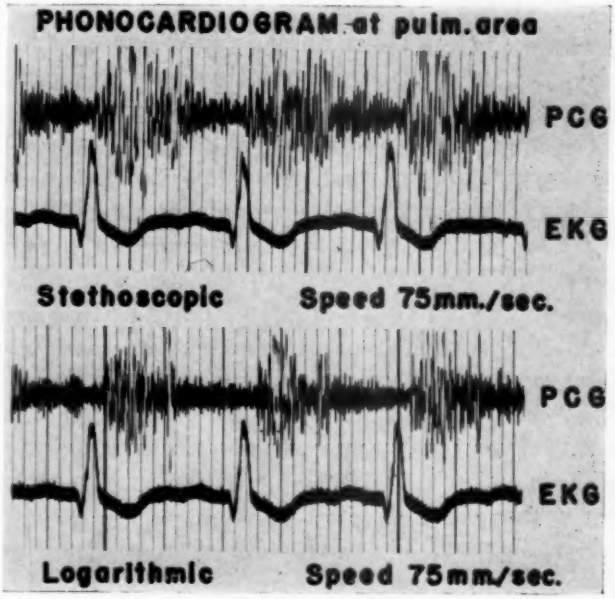


Fig. 3.—The phonocardiogram shows both systolic and diastolic murmurs.

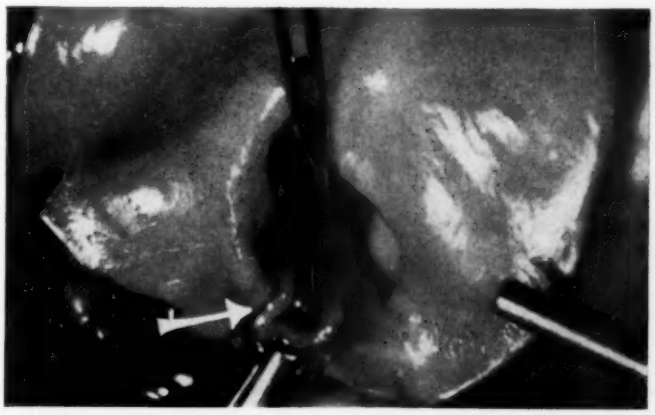


Fig. 4.—The arrow points to the enlarged, thickened noncoronary cusp which was inferiorly displaced but which has been pulled up so that it can be better visualized.

Pathologic Report.—(Autopsy was performed by Dr. Howard Fink.) "One centimeter defect in membranous ventricular septum. Hypertrophy and inferior displacement of the noncoronary cusp of the aortic valve" (Fig. 4) "with moderate aortic insufficiency and patent guarded foramen ovale. Dilatation and hypertrophy of the heart, 310 grams" (Normal, 96 grams).

DISCUSSION

Clinically, ventricular septal defect is characterized by a loud systolic murmur often accompanied by a systolic thrill at the left sternal border. A loud, accentuated P_2 and electrocardiographic evidence of right ventricular hypertrophy usually indicate that there is an accompanying significant degree of pulmonary hypertension. Once a continuous machinery-like murmur or a to-and-fro murmur is heard over the pulmonic area, the following differential diagnoses should be considered: patent ductus arteriosus,[19] aortic septal defect,[20,21] ventricular defect with or without aortic regurgitation, ruptured sinus of Valsalva,[22] aortic stenosis and regurgitation, pulmonary arteriovenous fistula, fistula of the chest wall, collateral arterial circulation, pulmonary anomalous venous drainage, coronary arteriovenous fistula,[23] anomalous coronary artery,[24] and arteriovenous aneurysm on the pulmonary artery.[25] Although most of these possibilities are not difficult to differentiate, they occasionally become a serious diagnostic problem. Once a patent ductus arteriosus is not actually catheterized or is excluded by thoracotomy, and the physiologic findings of large ventricular L-to-R shunt, wide systemic pulse pressure, and continuous pulmonic murmur remain, the following conditions must be considered: (1) ventricular septal defect with aortic septal defect, (2) ventricular septal defect with aortic regurgitation, (3) ruptured sinus of Valsalva with or without ventricular septal defect, and (4) aortic septal defect with pulmonary regurgitation.

Selective angiography with high-speed filming may either give some clue or rule out significant aortico-pulmonary communication,[20] if aortic regurgitation is not complicating the picture. The phonocardiogram is not diagnostic, particularly if there is marked pulmonary hypertension.

SUMMARY

Only 7 cases of ventricular septal defect with aortic incompetence have been catheterized and reported in the literature. This is the eighth case, a report of one of the rarer complications of ventricular septal defect, namely, aortic incompetence due to laxity of the noncoronary aortic cusp. A brief summary of ventricular septal defect and differential diagnosis are given.

We are indebted to Herbertine Clark, Donna Sims, Lavina Goering, Eleanor Lane, and Jo Ann Clifford for their technical assistance.

REFERENCES

1. Roger, H.: Bull. Acad. méd., Paris **8**:1074, 1879.
2. Laubry, C., and Pezzi, C.: Traité des Maladies Congenitales de Coeur, Paris, 1921, J. B. Bailli'ere et fils.
3. Laubry, C., Routier, D., and Soulié, P.: Rev. de méd., Paris **50**:439, 1933.
4. Taussig, H. B., and Semans, J. N.: Bull. Johns Hopkins Hosp. **66**:156, 1940.
5. Allen, A. C.: Am. Heart J. **21**:667, 1941.
6. Taussig, H. B.: Congenital Malformations of the Heart, New York, 1947, Commonwealth Fund.
7. Hurst, W. W., and Schemm, F. R.: Am. Heart J. **36**:144, 1948.
8. Soulié, P., Routier, D., and Bernal, P.: Arch. mal. coeur **42**:765, 1949.
9. Morgan, E. H., and Burchell, H. B.: Proc. Staff Meet. Mayo Clinic **25**:69, 1950.
10. Ash, R., and Murphy, L.: J. Pediat. **37**:249, 1950.
11. Danaraj, T. J.: Brit. Heart J. **18**:279, 1956.

12. Gotzsche, H.: Congenital Heart Disease, Copenhagen, 1952, Munskgaard.
13. Gross, R. E.: Am. J. Med. **12**:472, 1952.
14. Gross, R. E.: The Surgery of Infancy and Childhood, Philadelphia, 1953, W. B. Saunders Co.
15. Edwards, J. E.: An Atlas of Congenital Anomalies of the Heart and Great Vessels, Springfield, Ill., 1954, Charles C Thomas.
16. Wood, P., Magidson, O., and Wilson, P.A.O.: Brit. Heart J. **16**:387, 1954.
17. Baylis, J. H., Campbell, M., Gilmore, H. R., and Hudson, R.: Guy's Hosp. Rep. **104**:114, 1955.
18. Winchell, P., and Bashour, F.: Am. J. Med. **20**:361, 1956.
19. Gibson, G. A.: Edinburgh M. J., n.s. **8**:1, 1900.
20. Gasul, B. M., Fell, E. H., and Gasas, R.: Circulation **4**:251, 1951.
21. Dodds, G. H., and Hoyle, C.: Brit. Heart J. **11**:390, 1949.
22. Lin, T. K., Crockett, J. E., and Dimond, E. G.: AM. HEART J. **51**:445, 1956.
23. Paul, O., Sweet, R. H., and White, P. D.: AM. HEART J. **37**:441, 1949.
24. Davis, C., Jr., Dillon, R. F., Fell, E. H., and Gasul, B. M.: J.A.M.A. **160**:1047, 1956.
25. Biorch, G., and Crafoord, C.: Thorax **2**:65, 1947.

CONGENITAL ABSENCE OF THE HEPATIC PORTION OF THE INFERIOR VENA CAVA

ROBERT F. GROVER, M.D., PH.D., RAYMOND R. LANIER, M.D., PH.D., JAMES K. LOWRY, M.D., AND S. GILBERT BLOUNT, JR., M.D.

DENVER, COLO.

MAJOR anomalies of the inferior vena cava are rare, and to our knowledge there are only 24 reported cases in which the hepatic portion of this vessel was completely absent, although most assuredly there must be others that have not been reported. Of these cases, 5 were diagnosed ante mortem by means of venous angiography. A case is here presented in which the anomaly was demonstrated by venous angiocardiography, and subsequently confirmed at necropsy.

European anatomists of the nineteenth century, in their enthusiastic description and classification of structural anomalies of the human body, contributed many of the existing reports of absence of the hepatic portion of the inferior vena cava. In 1835, five of the known cases of this venous anomaly were described by Stark, as quoted by Reagan.[1] A century later, when the literature on this subject was thoroughly reviewed by Huseby and Boyden,[2] their case brought the total number to only 15. Latimer and Virden[3] published an additional description of this anomaly in 1944. Taussig[4] stated in her book that she had encountered only 1 example of this condition. In 1951, Effler and associates[5] described a variation of this anomaly in which a persistent left inferior vena cava was continuous with the right azygos vein, while the hepatic vein emptied directly into the right atrium. The most recent account of absence of the hepatic portion of the inferior vena cava was published by Druepple[6] in 1957, in his description of a case with multiple major cardiovascular anomalies.

With the advent of angiocardiography, a technique became available for diagnosing the presence of this anomaly during life. Stackelberg and associates[7] published the first 2 angiocardiographic demonstrations of this condition in 1952. An additional 2 cases were demonstrated by Downing[8] in 1953, while a fifth case was illustrated by Kjellberg[9] in 1955. The following case was also discovered by venous angiocardiography, and was subsequently confirmed by post-mortem examination.

CASE REPORT

J. M., a white female infant, lived only 18 weeks. She was the product of an uneventful first pregnancy and normal delivery, weighing 3,000 grams at birth. At the age of 2 weeks, tachypnea was first observed, but she was considered normal otherwise. Periods of cyanosis with crying

From the Cardiovascular Laboratory and the Department of Medicine, and the Departments of Radiology and Pathology, University of Colorado Medical Center, Denver, Colo.

Received for publication June 11, 1957.

and after feeding developed at the age of 6 weeks. A murmur was first reported at this time, and she was hospitalized for treatment of congestive heart failure. Some improvement followed digitalization. However, her cyanosis became more persistent until she required oxygen continuously.

Physical examination at this time revealed a small, poorly developed female infant, with generalized cyanosis when out of oxygen. All peripheral pulses were full, and the precordium was not overly active. A Grade 3 blowing systolic murmur was heard maximum in the third intercostal space, to the left of the sternum. The liver was enlarged to 4 cm. below the right costal margin.

On fluoroscopy, an enormous heart was noted, nearly filling the entire thoracic cavity (Fig. 1). The pulmonary vascularity was considered to be increased. Combined ventricular hypertrophy was the interpretation of the electrocardiogram. From these findings, the clinical impression was transposition of the great vessels, or possibly a true truncus arteriosus.

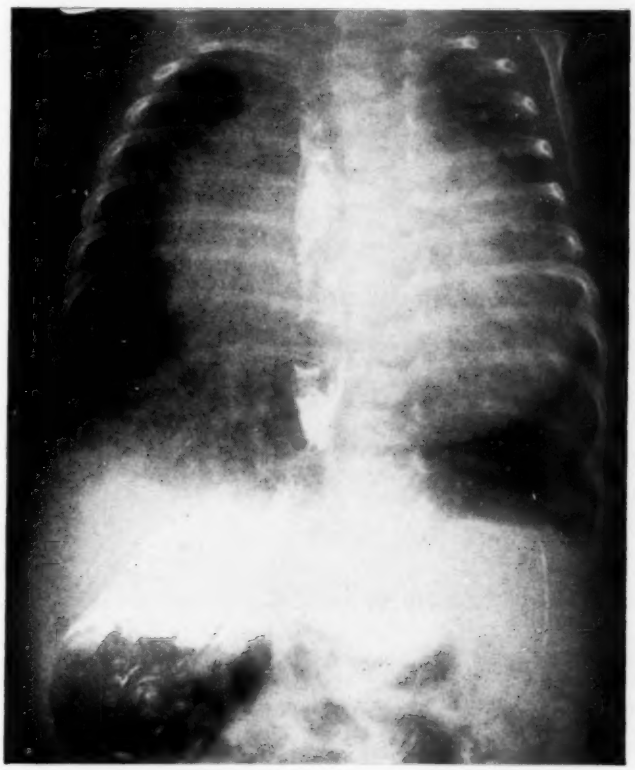


Fig. 1.—Posteroanterior roentgenogram of the chest showing marked enlargement of the heart and, incidentally, dextroposition of the stomach.

Venous angiocardiography was performed by the injection of 4 c.c. of 70 per cent Urokon into the left iliac vein by means of a polyethylene catheter introduced via the saphenous vein. The column of radio-opaque medium ascended without interruption close to the spine to the superior mediastinum, where it arched forward to enter the superior vena cava. It then descended into the right atrium, filling this structure, and was soon seen refluxing into the hepatic veins (Fig. 2). No structure was visualized which could be interpreted as being the inferior vena cava entering the right atrium. From the right atrium, the Urokon promptly appeared in the aorta, and almost simultaneously the pulmonary arteries were visualized. These films were interpreted as being compatible with the diagnosis of transposition of the great vessels.

While this procedure was well tolerated, the child's general condition remained poor, and she died 10 days later, weighing only 3,680 grams.

Multiple congenital anomalies were found at autopsy. The iliac veins joined to form a single postrenal vena cava. This structure received the renal veins in the normal manner, and then, following a course adjacent to the right side of the spinal column, penetrated the diaphragm and ascended past the heart to the level of the root of the right lung, where it arched anteriorly to join the superior vena cava. From the liver, two large hepatic veins passed through separate

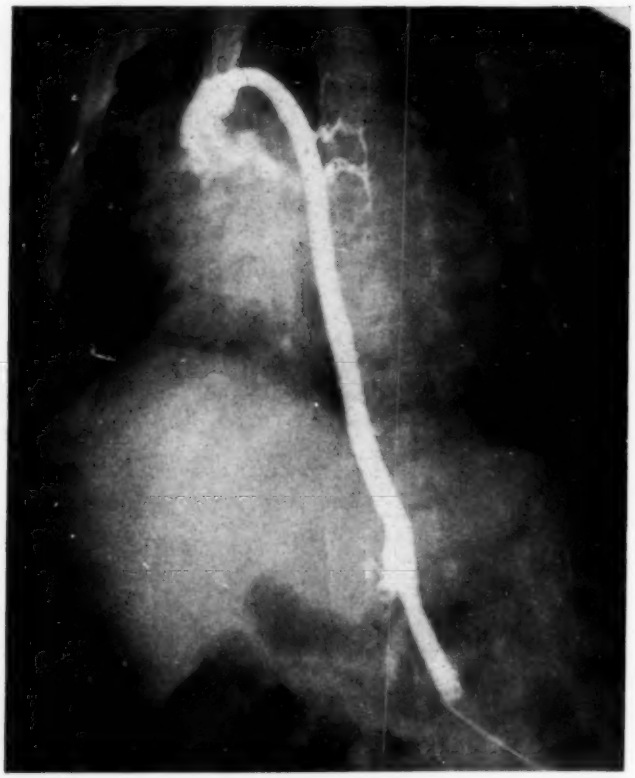


Fig. 2.—Left anterior oblique roentgenogram. Urokon has been injected into the caudal inferior vena cava. The azygos vein is outlined as a direct continuation of this vessel, and arches anteriorly to empty into the superior vena cava and right atrium.

openings in the diaphragm to enter the right atrium directly. Thus, the hepatic portion of the inferior vena cava was completely absent; absolutely no communication existed between the hepatic veins and the caval-azygos structure described above (Fig. 3).

The heart, while grossly enlarged, was situated normally in the chest. Both right atrium and right ventricle were markedly dilated, while the left atrium and ventricle were rudimentary. An atrial septal defect as well as a small ventricular septal defect were present. Not only did the right atrium receive the superior vena cava from above and the two hepatic veins from below, but all four pulmonary veins emptied via separate channels into this large chamber (Fig. 3). The pulmonary artery originated from the right ventricle, and the aorta from the left ventricle, in the normal fashion. In addition, the ductus arteriosus was widely patent.

While a true situs inversus of the abdominal organs was not present, the stomach was located on the right below a normally situated liver, the duodenum was on the left, and four small spleens were in the right lower quadrant. The portal venous system was normal.

Fig. 3.—Posterior aspect of the abdominal and thoracic viscera. The lobulated kidneys are seen in the lower right. From these, the renal veins empty into the inferior vena cava (*IVC*), which continues without interruption as the azygos vein (*AzV*). This arches over the root of the right lung to join the superior vena cava (*SVC*). Two large hepatic veins (*HV*) drain the major lobes of the liver, and pass directly into the large right atrium (*RA*). The four pulmonary veins are also seen emptying into this large chamber. In the upper left, the prominent diagonal vessel is the aorta, displaced for clarity. Two spleens are on the lower left, and drain via the portal vein (*PV*) into the liver.

DISCUSSION

From a brief and simplified review of the embryologic development of the inferior vena cava, the anomalous absence of its hepatic portion is readily understood. Initially, blood drains from the trunk of the embryo by way of the paired dorsal longitudinal posterior cardinal veins. As the mesonephric ridges develop, a pair of venous channels forms on their ventral medial surfaces; these are the subcardinal veins, and drain into the cranial portion of the posterior cardinals. An increasing volume of blood is carried by the dilating subcardinal veins, thus diminishing the flow in the posterior cardinals, which eventually atrophy except for their cranial portions.

Next, a communication develops between the right subcardinal vein and the hepatic veins. This provides a new and more direct route to the heart. Consequently, this channel enlarges rapidly, while the cephalic portion of the subcardinal diminishes in size. This pattern persists in the adult; the direct route for blood from the caudal portion of the body and the kidneys to the heart is by

way of the hepatic portion of the inferior vena cava, while the right subcardinal vein is represented by the azygos vein, which arches forward to empty into the superior vena cava by the only remaining portion of the original posterior cardinal vein. Such is the sequence of events as described by McClure and associates,[10,11] although Seib[12] has indicated that it may be more complex.

Considering the complicated interplay between the various venous systems that contribute to the entire adult inferior vena cava, it is surprising that major anomalies in this area are not more common. In the case presented here, it would appear that the communication failed to develop between the right subcardinal vein and the hepatic vein. Therefore, a large volume of blood continued to flow through the subcardinal vein to the superior vena cava. At birth, this channel was represented by the large azygos vein, which was a direct continuation of the prerenal inferior vena cava. Independently, the hepatic veins emptied directly into the inferior portion of the right atrium.

SUMMARY

Complete absence of the hepatic portion of the inferior vena cava was fortuitously demonstrated by venous angiocardiography in an infant with severe cyanotic congenital heart disease. On subsequent post-mortem examination, it was possible to investigate thoroughly this unusual anomaly. The probable developmental basis for this condition has been discussed.

REFERENCES

1. Reagan, F. P.: Quart. Rev. Biol. **4**:179, 1929.
2. Huseby, R. A., and Boyden, E. A.: Anat. Rec. **81**:537, 1941.
3. Latimer, H. B., and Virden, H. H.: J. Kansas M. Soc. **45**:346, 1944.
4. Taussig, H. B.: Congenital Malformations of the Heart, New York, 1947, The Commonwealth Fund, p. 317.
5. Effler, D. B., Greer, A. E., and Siters, E. C.: J.A.M.A. **146**:1321, 1951.
6. Druepple, L. G.: Am. Heart J. **53**:790, 1957.
7. Stackelberg, B., Lind, J., and Wegelius, C.: Cardiologia **21**:583, 1952.
8. Downing, D. F.: Pediatrics **12**:675, 1953.
9. Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B.: Diagnosis of Congenital Heart Disease, Chicago, 1955, Year Book Publishers, Inc., p. 10.
10. McClure, C. F. W., and Butler, E. G.: Am. J. Anat. **35**:331, 1925.
11. McClure, C. F. W., and Huntington, G. S.: Am. Anat. Mem. No. 15, 1929, pp. 1-55.
12. Seib, G. A.: Am. J. Phys. Anthropol. **19**:39, 1934.

Book Review

FUNDAMENTALS OF CLINICAL FLUOROSCOPY. By Charles B. Storch, M.D., Ed. 2, revised and enlarged, New York, 1957, Grune & Stratton. Price $8.75.

It goes without saying that in the present era in which radiology plays such an important part in the practice of medicine—a part which will increase progressively as time goes on—the need for a good fundamental textbook on radiology for medical and postgraduate students, especially one showing the value of fluoroscopy, is of the utmost importance. Similarly, it hardly need be stressed that a book describing a modality whose use is fraught with so much danger to both patient and radiologist should devote adequate space to a detailed description of the well-established principles of this science about which no dispute amongst the specialists in the field has arisen. Any book which attempts to separate fluoroscopy and x-ray film interpretation must of necessity fall short of its goal.

Many of the subjects to which the author has given special prominence appear to be inadequately covered. To cite a few examples:

Regarding congenital heart disease (1) he does not even mention the entity of interventricular septal defect, and (2) he states that in interatrial septal defect the fluoroscopic findings are definitely characteristic. However, it is my experience and that of many other radiologists that in any disease with a left-to-right shunt, such as interventricular septal defect, interatrial septal defect, and patent ductus arteriosus, the best observers may have difficulty in distinguishing these one from another. It is only in the light of clinical findings that one can come to a definite conclusion. In coarctation of the aorta he states (3) that the aortic knob is always small, while, as a matter of fact, this is only so in the infantile type of this condition: in the adult type of coarctation of the aorta (which the author ignores entirely) the aortic knob is often normal. In writing of pericardial effusion and its differentiation from a dilated heart, he states (4) that the absence of lateral and posterior displacement of the esophagus is in favor of a diagnosis of pericardial effusion, while such authorities as Shanks and Kerley state that it is common to observe displacement of the esophagus to the right and posteriorly in pericardial effusion.

In discussing the colon the author states, on page 239, that no definite diagnosis can be made on the fluoroscopic screen in the examination of the pathologic colon. Most radiologists feel that this is only partially true, since in such diseases as diverticulitis, fluoroscopic demonstration of irritability of the colon affords a clue to the diagnosis. On page 250, Fig. 290, he states that one half to two thirds of the cecal diameter usually equals the diameter of the descending colon. Strangely enough, the figure he presents is the reproduction of a *normal* colon, and he states that the diameter of this colon is less than the normal limit, and that this—together with increased haustral markings—can be taken as evidence of a spastic descending colon! This, of course, is erroneous and very misleading, since the diameter of the normal colon differs in practically every person. In his chapter on the colon he omits to mention the fluoroscopic and film findings in diverticulitis—a very common disease of the colon.

In the section on the esophagus in describing the findings in cardiospasm, he omits to mention the jetlike action of the barium as it passes from the esophagus into the stomach: this is one of the commonest fluoroscopic findings in cardiospasm. Neither does the author adequately cover the physiopathology of this condition. In describing the Plummer-Vinson syndrome, he completely ignores the characteristic and diagnostic fluoroscopic finding of a postcricoid web on the anterior wall of the esophagus.

On page 53, there is a reproduction of a radiograph purporting to show an enlarged thymus gland in a child. This, however, is actually a classical "sail" shadow in a normal thymus gland.

His chapter on protection is fairly adequate, but the figures he employs show the use of a 14 x 17 cm. screen, a size which is fraught with danger and the use of which is deplored by the majority of experienced radiologists. Moreover, this book does not contain the physical and biophysical principles of radiology which should be thoroughly well understood before any attempt is made by physician or postgraduate student to perform fluoroscopy.

The reproductions in this book are poor from a technical standpoint.

While these are only a few of the inadequacies and inaccuracies of this so-called textbook on clinical fluoroscopy, their number and variety throughout the book is such as to render it, in my opinion, practically useless as a textbook for the medical and postgraduate student studying the science of radiology as a diagnostic method.

F. R. McD.

Announcement

THE CHICAGO HEART ASSOCIATION will sponsor a CONFERENCE ON PULMONARY CIRCULATION to be held Thursday, Friday, and Saturday, March 20 to 22, 1958, at the Palmer House, Chicago.

Introductory sessions will be devoted to the physiology, anatomy, and pathology of the pulmonary circulation, with special emphasis on methods of clinical study. Later sessions will cover the pulmonary circulation in congenital heart disease, primary lung disease, and acquired heart disease.

Among the distinguished visitors who are accepting major responsibility in the planning and execution of the conference are Dr. Julius Comroe, University of Pennsylvania Graduate School of Medicine, Dr. Howard Burchell and Dr. Jesse Edwards of the Mayo Clinic, Rochester, Minn., Dr. Paul Wood from the Institute of Cardiology, London, and Dr. Lars Werkö of Goteborgs Universitet, Gothenburg, Sweden.

It is the objective of the conference to bring together major contributors to this controversial field. Each participant will present his own recent work, and opportunity will be offered for discussion. The meeting will be open to physicians and scientists.

Address: Chicago Heart Association, 69 West Washington St., Chicago 2, Ill.